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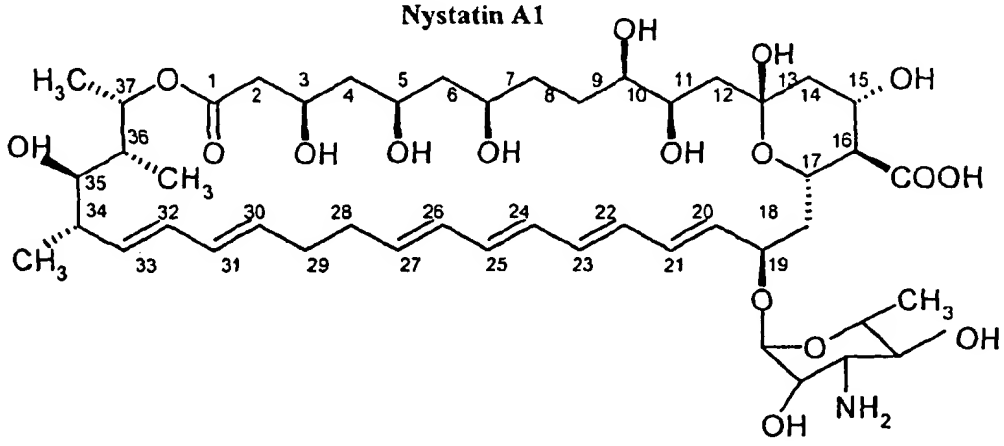
(54) Title: NOVEL GENES ENCODING A NYSTATIN POLYKETIDE SYNTHASE AND THEIR MANIPULATION AND UTILITY

Nystatin A1



(57) Abstract: The invention provides a nucleic acid molecule comprising: (a) a nucleotide sequence as shown in SEQ ID No. 35; or (b) a nucleotide sequence which is the complement of SEQ ID No. 35; or (c) a nucleotide sequence which is degenerate with SEQ ID No. 35; or (d) a nucleotide sequence hybridising under conditions of high stringency to SEQ ID No. 35, to the complement of SEQ ID No. 35, or to a hybridisation probe derived from SEQ ID No. 35 or the complement thereof; or (e) a nucleotide sequence having at least 80 % sequence identity with SEQ ID No. 35; or (f) a nucleotide sequence having at least 65 % sequence identity with SEQ ID No. 35 wherein said sequence preferably encodes or is complementary to a sequence encoding a nystatin PKS enzyme or a part thereof. Also provided are part of such molecules and polypeptides (and parts thereof) encoded by such a nucleic acid molecule, and the use of such molecules and polypeptides in facilitating nystatin biosynthesis and in the synthesis of nystatin derivatives and novel polyketide as macrolide structures.

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GENE CLUSTER ENCODING A NYSTATIN POLYKETIDE SYNTHASE AND ITS MANIPULATION AND UTILITY

The present invention relates to the cloning and sequencing of the gene cluster encoding a modular polyketide synthase enzyme involved in the biosynthesis of the macrolide antibiotic nystatin. The invention thus relates to novel genes and nucleic acid molecules encoding proteins/polypeptides exhibiting functional activities involved in nystatin biosynthesis, such functional proteins/polypeptides themselves, and their uses both in facilitating nystatin biosynthesis and in the synthesis of nystatin derivatives and novel polyketide or macrolide structures.

Polyketides are natural products synthesized by microorganisms, many of which have applied potential as pharmaceuticals or as agricultural or veterinary products. Examples of polyketides used in medical treatments include the antibiotics erythromycin (antibacterial), nystatin (antifungal), avermectin (antiparasitic), rapamycin (immunosuppressant) and daunorubicin (antitumor). The Gram-positive bacteria *Streptomyces* are the main producers of polyketides, and the genetics and biochemistry of polyketide biosynthesis in these organisms are relatively well characterized (Hopwood *et al.*, Chem. Rev. v. 97: 2465-2497 (1997)). Macrolide polyketide compounds are formed via repeated condensations of simple carboxylic acids by modular (type I) polyketide synthases (PKS) in a manner similar to fatty acid biosynthesis. The modular hypothesis proposed by Donadio *et al.* Science, v. 252: 675-679 (1991) suggested that type I PKSs are organized in repeated units (modules), each of which is responsible for one condensation cycle in the synthesis of a polyketide chain. This was proven to be correct by

manipulations of PKSs type I genes resulting in predictable changes in the chemical structures of macrolides. Beside condensation of the next carboxylic acid onto the growing polyketide chain, ensured by the catalytic activity of the β-ketoacyl synthase (KS) domain, modules of PKSs type I may contain domains with β-ketoreductase (KR), dehydratase (DH) and enoyl reductase (ER) activities, which determine the reduced state of incorporated extender units. The acyltransferase (AT) and acyl carrier protein (ACP) domains present in each module are responsible for the choice of extender unit and retention of the growing polyketide chain on the PSK, respectively. Upon completion of synthesis, the polyketide chain is released from PKSs via action of a thioesterase (TE), that is probably also involved in cyclization of the final product. Thus, PKSs type I represent an assembly line for polyketide biosynthesis, that can be manipulated by changing the number of modules, their specificities towards carboxylic acids, and by inactivating or inserting domains with reductive activities (Katz, Chem. Rev., v. 97, 2557-2575, 1997). After the polyketide moiety of a macrolide is synthesized and cyclized to form a macrolactone ring, it is usually modified via hydroxylation, glycosylation, methylation and/or acylation. These modifications are believed to be crucially important for the biological activities of macrolides.

The genes for macrolide antibiotic biosynthesis in *Streptomyces* are organized in clusters, and a number of such clusters have already been identified. Exploitation of recombinant DNA technology has made it possible to isolate complete antibiotic biosynthetic gene clusters by screening the gene libraries with DNA probes encoding PKSs (Schwecke *et al.*, Proc. Natl. Acad Sci. USA, v. 92: 7839-7843, 1995). The molecular cloning and complete DNA sequencing has been described

for several macrolide antibiotic gene clusters of *Streptomyces*, including those for avermectin, pikromycin and rapamycin (Ikeda *et al.*, Proc. Natl. Acad. Sci. USA, v. 96: 9509-9514, 1999; Xue *et al.*, Proc. Natl. Acad. Sci. USA, v. 95: 1211-12116, 1998; Schwecke *et al.*, Proc. Natl. Acad. Sci. USA, v. 92: 7839-7843, 1995). Partial cloning and DNA sequencing of the gene cluster for the polyene macrolide antibiotic pimaricin has recently been reported (Aparicio *et al.*, J. Biol. Chem., v. 274: 10133-10139, 1999). However, a complete DNA sequence of genes for the biosynthesis of a polyene macrolide antibiotic with antifungal activity has not yet been disclosed. There is a need and desire to increase the repertoire of available antifungal antibiotics, and/or to improve upon the properties (e.g. efficacy, toxicity, etc.) of existing drugs. Hence the provision of new antifungal treatments, particularly those exhibiting new or improved properties would represent a considerable advance in the art.

The present invention is directed to this aim, and is based on the cloning and DNA sequencing of the nystatin biosynthesis gene cluster. This provides the first example of the identification of such antifungal antibiotic biosynthesis genes, as well as a tool for genetic manipulation in order to modify the properties of nystatin and/or the producing organism, or to obtain novel potentially useful compounds.

The polyene antifungal antibiotic nystatin A1, the complete stereostructure of which (see Fig. 1) has been determined by Lancelin & Beau, Tetrahedron Lett, v. 30: 4521-4524, (1989), is produced by *Streptomyces noursei* ATCC11455. From the structure of the nystatin molecule, which belongs to the class of macrolide compounds, we predicted that its polyketide backbone is synthesized by a PKS type I enzyme. Based on this assumption, and as described in the Examples below, a genomic library of *Streptomyces noursei* ATCC11455 was screened using a

specially designed probe obtained by PCR using primers based on conserved amino acid sequences within known β-ketoacyl synthase (KS) and acyl carrier protein (ACP) domains of known modular PKS enzymes. This led to the identification of a number of clones or fragments which we have sequenced and shown to contain parts or portions of the nystatin PKS gene cluster. We have further shown that alteration of the fragment sequences to inactivate the encoded product leads to abrogation of nystatin biosynthesis (see Example 1 below), thereby confirming the requirement of the identified PKS for nystatin biosynthesis. Subsequent work on the clones/fragments has lead to the sequencing of the PKS gene cluster, and the identification of the different modules and enzymatic domains, regulatory regions etc, within it.

Furthermore, as will be described in more detail below, we have shown that manipulations of functional DNA sequences within the novel nystatin PKS gene cluster which we have identified, have led to the synthesis of novel molecular structures, e.g. nystatin derivatives with improved function. This opens up the exciting possibility of manipulating the nystatin A1 PKS gene cluster to obtain not only beneficial new nystatin derivatives, but also to improve and facilitate the biosynthetic production process (for example to improve yield, or production conditions, or to expand the range of available host cells) or to provide novel compounds with new activities and/or properties.

More particularly, two primary regions (or "parts" or "portions") of the nystatin PKS gene cluster were initially identified and sequenced, together representing approximately 80% of the nystatin PKS gene cluster, and the functional sequences within said regions (e.g. PKS genes, regulatory regions etc, as well as functional gene products, enzymatic domains etc.) have been identified and characterised.

The first region ("Region 1"), which we have termed

"Nys 1" and the complete DNA sequence of which is shown in SEQ ID No. 1, has been shown to contain a number of PKS or associated genes or regulatory regions, and 13 separate "features" or open reading frames (ORFs) have been identified (the amino acid sequences of the translation products of which are shown in SEQ ID Nos. 3 to 15 respectively).

The second region ("Region 2"), which we have termed "Nys 2", and the complete coding sequence of which is shown in SEQ ID No. 2, also comprises a number of "functional" regions, and 5 separate "features" or ORFs have been identified, the amino acid sequences of the translation products of which are shown in SEQ ID Nos. 16 to 20 respectively.

Nys 1 and Nys 2 (i.e. SEQ ID Nos. 1 and 2 and the sequences they encode) are the subject of British Patent Application No. 0002840.7 filed on 8 February 2000.

Subsequent sequencing efforts have led to the determination of the sequence of the DNA spanning the gap between SEQ ID Nos. 1 and 2, and the identification of novel genes in this region. In addition, the partial gene sequences contained in SEQ ID Nos. 1 and 2 encoding the gene products NysI (SEQ ID No. 20) and NysDII (SEQ ID Nos. 3) (see further below) have been completed (see new SEQ ID Nos. 36 and 37 respectively - see further below). Thus, these sequencing efforts have led to the identification and sequencing of the DNA region encompassing the entire nystatin PKS gene cluster, and the identification and characterisation of the functional sequences within this region.

The complete coding sequence for (i.e. the complete nucleotide sequence encoding) the nystatin biosynthetic gene cluster is shown in SEQ ID No. 35. This has been shown to contain a number of PKS or associated genes or regulatory regions, and 23 separate "features" or ORFs have been identified (the amino acid sequences of the translation products of which are shown in SEQ ID Nos. 2

to 19, and 36 to 42 respectively).

The complete coding sequence for (i.e. the complete nucleotide sequence encoding) the nystatin biosynthetic gene cluster, as shown in SEQ ID No. 35, is the subject of British Patent Application No. 0008786.6 filed on 10 April 2000 and British Patent Application No. 0009387.2 filed on 14 April 2000.

In one aspect, the present invention thus provides a nucleic acid molecule comprising:

(a) a nucleotide sequence as shown in SEQ ID No. 35; or

(b) a nucleotide sequence which is the complement of SEQ ID No. 35; or

(c) a nucleotide sequence which is degenerate with SEQ ID No. 35; or

(d) a nucleotide sequence hybridising under conditions of high stringency to SEQ ID No. 35, to the complement of SEQ ID No. 35, or to a hybridisation probe derived from SEQ ID No. 35 or the complement thereof; or

(e) a nucleotide sequence having at least 80% sequence identity with SEQ ID No. 35; or

(f) a nucleotide sequence having at least 65% sequence identity with SEQ ID No. 35 wherein said sequence preferably encodes or is complementary to a sequence encoding a nystatin PKS enzyme or a part thereof.

A "nystatin PKS enzyme" is defined further below, but briefly in the context of section (f) above means an enzyme or protein or polypeptide that is functional in the synthesis, transport or transfer of a macrolide antibiotic or polyketide moiety, preferably nystatin or a nystatin derivative or nystatin-related molecule.

In a further aspect, the present invention also provides a nucleic acid molecule comprising:

(a) a nucleotide sequence as shown in SEQ ID No. 1 and/or in SEQ ID No. 2; or

(b) a nucleotide sequence which is the complement of SEQ ID No. 1 and/or SEQ ID No. 2; or

(c) a nucleotide sequence which is degenerate with SEQ

ID No. 1 and/or SEQ ID No. 2; or

(d) a nucleotide sequence hybridising under conditions of high stringency to SEQ ID No. 1 and/or SEQ ID No. 2, to the complement of SEQ ID No. 1 and/or SEQ ID No. 2, or to a hybridisation probe derived from SEQ ID Nos. 1 and/or 2 or the complements thereof; or

(e) a nucleotide sequence having at least 65% sequence identity with SEQ ID No. 1 and/or SEQ ID No. 2, wherein said sequence preferably encodes or is complementary to a sequence encoding a nystatin PKS enzyme or a part thereof.

A nucleic acid molecule of the invention may be an isolated nucleic acid molecule (in other words isolated or separated from the components with which it is normally found in nature) or it may be a recombinant or a synthetic nucleic acid molecule.

The nucleic acid molecule of the invention encodes (or comprises a nucleotide sequence encoding) the nystatin A1 PKS enzyme, or a portion thereof e.g. a sequence encoding a single domain, or comprises a nucleotide sequence in the nystatin A1 PKS gene cluster which is a functional or non-functional genetic element. More precisely, the nucleic acid molecule of the invention encodes one or more polypeptides, or comprises one or more genetic elements having functional activity in the synthesis of a macrolide antibiotic or a polyketide moiety, preferably nystatin or a nystatin derivative or nystatin-related molecule. Such functional activity may be enzymatic activity e.g. an activity involved in the synthesis or transport or transfer of a polyketide moiety or a macrolide molecule (this can be macrolide chain or ring synthesis or any step contributory thereto, or macrolide ring or polyketide chain modification etc) and/or it may be a regulatory activity, e.g. regulation of the expression of the genes or proteins involved in the synthesis, or regulation of the synthetic process, and/or it may be a

"transporter activity". Thus, included generally are also transport proteins involved in the transfer or transport of polyketide or macrolide moieties e.g. in the transport or efflux of the synthesised molecule within or out of the cell. Also included in this respect are glycosylation proteins which includes molecules involved in the biosynthesis and/or attachment of saccharides (e.g. mycosamine) to the macrolide or polyketide.

Whilst nucleotide sequences encoding a desired product are preferred according to the invention, also encompassed are nucleotide sequences comprising functional genetic elements such as promoters, promoter-operator regions, enhancers, other regulatory sequences etc. Thus, the nucleic acid molecule of the invention need not comprise the entire PKS gene cluster but may comprise a portion or part of it e.g. a part encoding a polypeptide having a particular function or a regulatory sequence. This may comprise one or more genes, and/or regulatory sequences, and/or one or more modules or, enzymatic domains, or non-coding or coding functional genetic elements (e.g. elements controlling gene expression, transcription, translation etc).

In one such aspect, the invention provides a nucleic acid molecule as defined above, wherein said nucleotide sequence of SEQ ID No. 35 (or variant thereof as defined in (b) to (f) above) does not include the portions of the molecule comprising ORF 1 (see Table 1 below). In other words, in this embodiment, the nucleotide sequence of SEQ ID No. 35 does not comprise nucleotides 124026 to 125222.

In another such aspect, the invention provides a nucleic acid molecule as defined above, wherein said nucleotide sequence of SEQ ID No. 35 (or variant thereof as defined in (b) to (f) above) does not include the portions of the molecule comprising ORF 2 (see Table 1 below). In other words, in this embodiment, the

nucleotide sequence of SEQ ID No. 35 does not comprise nucleotides 122812 to 123876.

In a further such aspect, the invention provides a nucleic acid molecule as defined above, wherein said nucleotide sequence of SEQ ID No. 35 (or variant thereof as defined in (b) to (f) above) does not include the portions of the molecule comprising *NysF* (see Table 1 below). In other words, in this embodiment, the nucleotide sequence of SEQ ID No. 35 does not comprise nucleotides 454 to 1191.

Alternatively, the invention provides nucleic acid molecules which contain a part of ORF 1, ORF 2 and/or *NysF*, or a modified sequence of ORF 1, ORF 2 and/or *NysF*, such that the expression or the function of the ORF 1, ORF 2 and/or *NysF* gene product is ablated.

Included within the scope of the invention are nucleotide sequences which hybridise to SEQ ID Nos. 1 or 2 or 35 or their complements, or to parts thereof (i.e. to hybridisation probes derived from SEQ ID Nos. 1 or 2 or 35 which are discussed in more detail below), under high stringency conditions and which preferably encode or are complementary to a sequence which encodes a nystatin PKS enzyme or part thereof. Conditions of high stringency may readily be determined according to techniques well known in the art, as described for example in Sambrook *et al.*, 1989, Molecular Cloning, A Laboratory Manual, 2nd Edition. Hybridising sequences included within the scope of the invention are those binding under non-stringent conditions (6 x SSC/50% formamide at room temperature) and washed under conditions of high stringency (e.g. 0.1 x SSC, 68°C), where SSC = 0.15 M NaCl, 0.015M sodium citrate, pH 7.2.

A hybridisation probe may be a part of the SEQ ID No. 1 or SEQ ID No. 2 or SEQ ID No. 35 sequence (or complementary sequence), which is of sufficient base length and composition to function to hybridise to sample or test nucleic acid sequences to determine

whether or not hybridisation under high stringency condition occurs. The probe may thus be at least 15 bases in length preferably at least 30, 40, 50, 75, 100 or 200 bases in length. Representative probe lengths thus include 30-500 bases e.g. 30-300, 50-200, 50-150, 75-100.

The hybridisation probe may be derived from a coding or non-coding, functional or non-functional part of the sequence (i.e. SEQ ID Nos. 1 or 2 or 35 or their complements), and may for example correspond to a gene or module or to an enzymatic domain, or a part thereof (e.g. the part encoding the active site) or to a sequence which links enzymatic domains or modules. Thus, the hybridisation probe may have functional activity in polyketide/macrolide synthesis as defined above.

Nucleotide sequence identity may be determined using the BestFit program of the Genetics Computer Group (GCG) Version 10 Software package from the University of Wisconsin. The program uses the local homology algorithm of Smith and Waterman with the default values: Gap creation penalty = 50, Gap extension penalty = 3, Average match = 10,000, Average mismatch = -9.000.

Nucleotide sequences according to the invention may exhibit at least 65%, 70%, 75%, 80%, 85%, 90%, 95% or 98% sequence identity with SEQ ID Nos. 1 or 2 or 35 and preferably encode or are complementary to a sequence which encodes a nystatin PKS enzyme or part thereof. Nucleotide sequences meeting the % sequence identity criteria defined herein may be regarded as "substantially identical" sequences.

Where the nucleic acid molecules of the invention are defined by reference to SEQ ID Nos. 1 and/or 2, the nucleic acid molecule of the invention may thus comprise a SEQ ID No. 1 or "SEQ ID No. 1-variant" sequence (i.e. a sequence complementary, or degenerate to SEQ ID No. 1 or a functionally equivalent variant such as a

hybridising or substantially identical sequence as defined above) or a SEQ ID No. 2 or "SEQ ID NO. 2-variant" sequence or both. Nucleic acid molecules comprising both a SEQ ID No. 1/SEQ ID NO. 1-variant sequence and a SEQ ID No. 2/SEQ ID NO. 2-variant sequence are preferred.

As referred to herein "functionally equivalent variants" or "functional equivalents" retain at least one function of the entity to which they are related (or from which they are derived), e.g. encode a protein with substantially the same properties, or exhibit substantially the same regulatory or other functional properties or activities.

As mentioned above, nucleic acid molecules comprising parts or portions (e.g. fragments) of the nucleotide sequences of SEQ ID No. 35 or of SEQ ID No. 1 and/or 2 (or their complementary, degenerate or functionally equivalent variants) are also included within the scope of the invention.

Such parts or portions of the PKS gene cluster advantageously may also be regarded as functional equivalents of the complete sequence. For example, the sequence portion or fragment may retain a functional activity as defined above, e.g. an enzymatic, regulatory, or transporter activity in polyketide or macrolide biosynthesis.

Conveniently, the part or portion of the PKS gene cluster (e.g. of SEQ ID No. 35, or 1 and/or 2) is at least 15 bases in length, more preferably at least 20, 25, 30, 35, 40, 50, 70, 100, 200, 300, 400, 500, 1000, 2000, 5000, 10,000, 15,000, 20,000, 30,000, or 50,000 bases. Representative fragment lengths thus include 15-50,000 bases e.g. 50-30,000 bases, or 100-20,000, 100-10,000 or 200-5,000, or 200-2,000. The part or portion may comprise or encode contiguous or non-contiguous nucleotide or amino acids.

Parts or portions of functional parts of the PKS

gene sequences are discussed in more detail below.

Parts or portions of the PKS gene cluster may also comprise the non-coding or non-functional part of the DNA molecule (or the nucleotide sequences), for example promoter or operator sequences, or linker sequences joining individual genes, modules or enzymatic domains. These may be contiguous or non-contiguous and will be discussed further below.

As mentioned above, a number of genes and ORFS within SEQ ID Nos. 35, 1 and 2 have been identified and such genes (or their complementary, degenerate or functionally equivalent variants as defined above) represent preferred "parts" or fragments of SEQ ID Nos. 35, 1 and 2. These are tabulated in Table 1 below:

Table 1

Molecule features of SEQ ID Nos. 35, 1 and 2 (the whole gene cluster sequence (125401 bp) Nys 1 (65140 bp) and Nys 2 (27541bp) respectively)

SEQ ID No. 35

Start	End	Gene	Description
1191	454 C	*nysF*	putative 4'-phsphopantheteine transferase
3092	1275 C	*nysG*	ABC transporter
4824	3070 C	*nysH*	ABC transporter
5122	6156	*nysDIII*	dGDP-mannose-4,6-dehydratase homolog
6338	34771	*nysI*	NysI PKS, modules 9-14
34792	51097	*nysJ*	NysJ PKS, modules 15-17
51155	57355	*nysK*	NysK PKS (module 18 + TE)
57503	58685	*nysL*	P450 monnoxygenase NysL
58980	58788 C	*nysM*	ferredoxin NysM

	60241	59047 C	*nysN*	P450 monooxygenase NysN
	61296	60240 C	*nysDII*	putative aminotransferase
	62837	61317 C	*nysDI*	putative UDP-glucoronosyltransferase
5	63067	67167	*nysA*	NysA PKS, loading module
	67213	76791	*nysB*	NysB PKS, modules 1 and 2
	76811	110101	*nysC*	NysC PKS, modules 3-8
	110521	111276	*nysE*	putative thioesterase
	111666	114566	*nysRI*	transcriptional activator
10	114590	117451	*nysRII*	putative transcriptional activator
	117441	120224	*nysRIII*	putative transcriptional activator
	120676	121308	*nysRIV* (short)	putative response regulator
15	120628	121308	*nysRIV* (long)	putative response regulator
	121997	122758	*nysRV*	putative repressor
	123876	122812 C	ORF2	putative transcriptional regulator
20	124026	125222	ORF1	putative peptidase (aminohydrolase)

Note: "C" indicates that the gene is encoded by the complement DNA strand.

nys 1 (SEQ ID No. 1)

Start	End	Gene	Description Name
1035	3 C	*nysD2*	putative aminotransferase
2447	1058 C	*nysD1*	putative UDP-glucuronosyl-transferase
2806	6904	*nysA*	nystatin PKS, loading module
6952	16528	*nysB*	nystatin PKS, modules 1 and 2

16550	49838	*nysC*	nystatin PKS, modules 3-8
50227	51013	*nysE*	putative thioesterase
51405	54303	*nysR1*	putative transcriptional activator 1
54329	57188	*nysR2*	putative transcriptional activator 2
57180	59961	*nysR3*	putative transcriptional regulator 3
60367	61045	*nysR4*	putative response regulator
61736	62495	*nysR5*	putative repressor
63615	62553 C	ORF2	putative transcriptional regulator
63765	64959	ORF1	putative peptidase (aminohydrolase)

nys 2 (SEQ ID No. 2)

Start	End	Gene	Description Name
1191	456 C	*nysF*	putative 4'-phosphopantheteine transferase
3092	1277 C	*nysG*	putative ABC transporter
4824	3072 C	*nysH*	putative ABC transporter
5122	6154	*nysD3*	putative GDP-mannose-4,6-dehydratase
6338	27541	*nysI*	nystatin PKS, modules 9-13(incomplete)

"C" in the table above refers to complementary strands.

It will be appreciated that *nys*D2, D1, A, B, C, E, R1 to R5, ORF1, ORF2 of SEQ ID No. 1 and *nys*F, G, H and D3, and the partial *nys*I sequences of SEQ ID No. 2, correspond to their named counterparts in SEQ ID No. 35, which represents the whole complete coding sequence for the gene cluster, and comprises the nucleotide sequences

of SEQ ID Nos. 1 and 2. There is however a difference in the nucleotide numbering as between the corresponding features in SEQ ID Nos. 2 and 35; for SEQ ID Nos. 1 and 2, the first nucleotide in the stop codon is recognised as the end of the gene, whereas for SEQ ID No. 35, the third nucleotide of the stop codon is recognised as the end of the gene. *nys*D1, D2 and D3 are also known as NysDI, DII and DIII, and *nys*R1 to R5 are also known as *nys*RI to RV.

As regards SEQ ID No. 1 (*nys1*) and the gene sequence *nysRI*, Table 1 shows this to comprise nucleotides 51405 to 54303. Further sequence analysis has revealed however that there are in fact two start codons, nucleotides 51405-51407 encoding GTG and nucleotides 51408-51410 encoding ATG. Accordingly, nucleotide 51408 of SEQ ID No. 1 represents an alternative start nucleotide for *nysRI*. ATG is preferred as a start codon to GTG, and consequently 51408 is regarded the start nucleotide in future references to *nysRI*. The start of *nysRI* in SEQ ID No. 35 is indicated in Table 1 above as the ATG codon, and the translation product of *nysRI* shown in SEQ ID No. 9 below is deduced from nucleotides 51408-54303 of SEQ ID No. 1. [In an alternative presentation of the NysRI translation product, wherein nucleotide 51405 of SEQ ID No. 1 is the start nucleotide, SEQ ID No. 9 is modified by the inclusion of an additional "first" amino acid, V].

As regards SEQ ID Nos. 35 and 1, and the gene sequence *nysRIV*, Table 1 shows this to comprise nucleotides 120676 to 121308 in SEQ ID No. 35 (nysRIV short). Further sequence analysis has revealed however that there are in fact two start codons, nucleotides 120676-120678 encoding GTG and nucleotides 120628-120630 encoding GTG. These start codons correspond to start codons in SEQ ID No. 1 for nysR4 at nucleotides 60367-60369 (as stated in Table 1) and 60415-60417. The

upstream GTG (120628-120630 in SEQ ID No. 35, which corresponds to 60367-60369 in SEQ ID No. 1) is preferred as a start codon (see Example 6), and consequently 120628 is regarded the start nucleotide in future references to *nysRIV*. The start of *nysRIV* in SEQ ID No. 35 is indicated in Table 1 above (nysRIV short) as the downstream start codon 120676-120678, and the deduced translation product of *nysRIV* named herein as "NysRIV short" is shown in SEQ ID No. 12. Table 1 also shows the alternative start codon of *nysRIV* (*nysRIV* long) in SEQ ID No. 35 as the upstream start codon 120628-120630. Thus a preferred alternative presentation of the NysRIV translation product, named herein "NysRIV (long)", is shown in SEQ ID No. 43.

Alternative representative parts of the SEQ ID No. 35, or 1 and/or 2 sequences include the nucleotide sequences between the respective "start" and "end" nucleotide positions, either individually or collectively.

The translation products of the respective "genes" have been deduced and the amino acid sequences are set out in the following SEQ ID Nos. shown below:

Gene Product	SEQ ID No.
NysD2(NysDII)(partial)	3
NysD1 (nysDI)	4
NysA	5
NysB	6
NysC	7
NysE	8
NysR1(NysRI)	9
NysR2(NysRII)	10
NysR3(NysRIII)	11
NysR4(NysRIV)(short)	12
NysR4(NysRIV)(long)	43
NysR5(NysRV)	13
ORF2	14

ORF1	15
NysF	16
NysG	17
NysH	18
NysD3(NysDIII)	19
NysI	20
NysDII(complete)	36
NysI(complete)	37
NysJ	38
NysK	39
NysL	40
NysM	41
NysN	42

SEQ ID Nos. 4, 10, 12, 13, 14, 16, 18, 41 and 43 show valine (V) as the first amino acid. According to practice in this field and conceptual translation of bacterial DNA, the first amino acid of a protein (translation product) is always methionine (M), regardless of the start codon. Accordingly, translation products and amino acid sequences of the present invention include not only SEQ ID Nos. 4, 10, 12, 13, 14, 16, 18, 41 and 43 as presented but also modifications of the aforesaid sequences in which the first V is replaced with M. References to SEQ ID Nos. 4, 10, 12, 13, 14, 16, 18, 41 and 43 below will be understood to include not only the sequences as presented, but also the said sequences wherein the first V is replaced with M.

Viewed from an alternative aspect, the present invention also provides a nucleic acid molecule comprising a nucleotide sequence encoding one or more amino acid sequences selected from SEQ ID Nos 3 to 20 or 36 to 43, or a nucleotide sequence which is complementary thereto or degenerate therewith.

Also provided are nucleic acid molecules comprising nucleotide sequences encoding one or more amino acid

sequences (i.e. polypeptides) which exhibit at least 60% sequence identity with any one of SEQ ID Nos. 3 to 20 or 36 to 43.

A further aspect of the invention provides a polypeptide encoded by a nucleic acid molecule of the invention as defined herein.

More particularly, this aspect of the invention provides a polypeptide comprising:

(a) all or part of an amino acid sequence as shown in any one or more of SEQ ID Nos. 3 to 20 or 36 to 43; or

(b) all or part of an amino acid sequence which has at least 60% sequence identity with any one or more of SEQ ID Nos. 3 to 20 or 36 to 43.

In particular the amino acid sequence may exhibit at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 98% identity with the polypeptide of any one of SEQ ID Nos. 3 to 20 or 36 to 43. Alternatively, the amino acid sequence may exhibit at least 70%, 75%, 80%, 85%, 90%, 95% or 98% similarity with the polypeptide of any one of SEQ ID Nos. 3 to 20 or 36 to 43. Amino acid (polypeptide) sequences meeting the % sequence identity or similarity criteria herein are regarded as "substantially identical". The polypeptide of the invention may be an isolated, purified or synthesized polypeptide. The term "polypeptide" is used herein to include any amino acid sequence of two or more amino acids i.e. both short peptides and longer lengths (i.e. polypeptides) are included.

Amino acid sequence identity or similarity may be determined using the BestFit program of the Genetics Computer Group (GCG) Version 10 Software package from the University of Wisconsin. The program uses the local homology algorithm of Smith and Waterman with the default values: Gap creation penalty = 8, Gap extension penalty = 2, Average match = 2.912, Average mismatch = -2.003.

A "part" of the amino acid sequence of any one of

SEQ ID Nos. 3 to 20 or 36 to 43 (or of a "substantially identical" sequence as defined above) may comprise at least 20 contiguous amino acids, preferably at least 30, 40, 50, 70, 100, 150, 200, 300, 400, 500, 1,000, 2,000, 5,000 or 10,000 contiguous amino acids.

The polypeptide, and preferably also the part thereof, is functionally active according to the definitions given above, e.g. is enzymatically active or has a regulatory or transport functional activity. The part may not itself be functionally active but may in some instances provide regions with functional properties of the whole, e.g. represent the active site or co-factor binding site required for enzymatic activity.

The studies described in the Examples below have characterised the nucleotide and polypeptide sequences of the invention and various functional regions within them have been identified. Such functional regions form separate aspects of the invention. For the various translation products (i.e. gene products of SEQ ID Nos. 3 to 20 or 36 to 43), these functional regions are summarised below in Table 2 below:

Table 2: Molecule Features of Translation Products of SEQ ID Nos. 3 to 20 and 36 to 43

(i) SEQ ID No.: 5
Translation Product Name : NysA

Start AA	End AA	Name	Description
8	430	KS[3]	KS domain, loading module
528	841	AT	AT domain, loading module
855	1055	DH	DH domain, loading module
1285	1359	ACP	ACP domain, loading module

(ii) SEQ ID No.: 6
Translation Product Name: NysB

Start	End	Name	Description
42	462	KS1	KS domain, module 1
578	897	AT1	AT domain, module 1 (mMCoA-specific)
911	1110	DH1	DH domain, module 1 (inactive)
1201	1447	KR1	KR domain, module 1
1484	1559	ACP1	ACP domain, module 1
1579	2004	KS2	KS domain, module 2
2117	2439	AT2	AT domain, module 2 (mMCoA-specific)
2453	2659	DH2	DH domain, module 2 (inactive)
2749	2996	KR2	KR domain, module 2
3025	3102	ACP2	ACP domain, module 2

(iii) SEQ ID No.: 7
Translation Product Name: NysC

Start	End	Name	Description
35	455	KS3	KS domain, module 3
546	858	AT3	AT domain, module 3
872	1073	DH3	DH domain, module 3
1381	1628	KR3	KR domain, module 3
1662	1735	ACP3	ACP domain, module 3
1757	2180	KS4	KS domain, module 4
2291	2603	AT4	AT domain, module 4
2617	2818	DH4	DH domain, module 4
3124	3371	KR4	KR domain, module 4
3407	3480	ACP4	ACP domain, module 4
3501	3924	KS5	KS domain, module 5

4032	4346	AT5	AT domain, module 5
4360	4561	DH5	DH domain, module 5
4953	5239	ER5	ER domain, module 5
5248	5495	KR5	KR domain, module 5
5528	5601	ACP5	ACP domain, module 5
5623	6046	KS6	KS domain, module 6
6166	6478	AT6	AT domain, module 6
6492	6704	DH6	DH domain, module 6
7038	7281	KR6	KR domain, module 6
7315	7388	ACP6	ACP domain, module 6
7408	7831	KS7	KS domain, module 7
7939	8253	AT7	AT domain, module 7
8267	8470	DH7	DH domain, module 7
8812	9086	KR7	KR domain, module 7
9120	9193	ACP7	ACP domain, module 7
9214	9637	KS8	KS domain, module 8
9758	10072	AT8	AT domain, module 8
10086	10289	DH8	DH domain, module 8
10657	10904	KR8	KR domain, module 8
10939	11012	ACP8	ACP domain, module 8

(iv) SEQ ID No.: 9
Translation Product Name: Nys R1

Start	End	Name	Description
42	49	P-loop	ATP/GTP binding site motif A
904	932	HTH	LuxR-type helix-turn-helix motif (DNA binding)

(N.B. In the alternative representation of NysR1 above, where nt 51405 of SEQ ID No. 1 is regarded as the start codon, these start and amino acid end numbers would each increase by 1.)

(v) SEQ ID No.: 10
Translation Product Name: NysR2

Start	End	Name	Description
902	930	HTH	LuxR-type helix-turn-helix motif (DNA binding)

(vi) SEQ ID No.: 11
Translation Product Name: NysR3

Start	End	Name	Description
26	47	LZ	Leucine zipper motif (DNA binding)
548	568	TM1	Transmembrane domain (putative)
583	610	TM2	Transmembrane domain (putative)
884	912	HTH	LuxR helix-turn-helix motif

(vii) SEQ ID No.: 12
Translation Product Name: NysR4 (short)

Start	End	Name	Description
97	104	P-loop	ATP/GTP binding site motif A
149	177	HTH	LuxR helix-turn-helix motif (DNA binding)

(viii) SEQ ID No.: 13
Translation Product Name: NysR5

Start	End	Name	Description
6	40	HTH	DeoR helix-turn-helix motif (DNA binding)

(ix) SEQ ID No.: 14
Translation Product Name: ORF2

Start	End	Name	Description
186	202	HTH	AsnC HTH motif signature

(x) SEQ ID No.: 17
Translation Product Name: NysG

Start	End	Name	Description
31	313	TM	Transmembrane regions
392	399	P-loop	ATP/GTP binding site
496	510	ABC	ABC transporters signature

(xi) SEQ ID No.: 18
Translation Product Name: NysH

Start	End	Name	Description
17	288	TM	Transmembrane regions
368	375	P-loop	ATP/GTP binding motif A
472	486	ABC	ABC transporters signature

(xii) SEQ ID No.: 20
Translation Product Name: NysI (partial)

Start	End	Name	Description
34	448	KS9	KS domain, module 9
572	890	AT9	AT domain, module 9
904	1123	DH9	DH domain, module 9
1443	1686	KR9	KR domain, module 9
1720	1793	ACP9	ACP domain, module 9
1813	2236	KS10	KS domain, module 10
2346	2664	AT10	AT domain, module 10
2678	2890	DH10	DH domain (inactive), module 10
2983	3229	KR10	KR domain, module 10
3266	3339	ACP10	ACP domain, module 10
3358	3780	KS11	KS domain, module 11
3898	4217	AT11	AT domain, module 11 (mMCoA-specific)
4231	4432	DH11	DH domain (inactive), module 11
4523	4770	KR11	KR domain, module 11
4806	4879	ACP11	ACP domain, module 11
4801	5325	KS12	KS domain, module 12
5432	5754	AT12	AT domain, module 12
5768	5977	DH12	DH domain (inactive), module 12
6068	6315	KR12	KR domain, module 12
6348	6421	ACP12	ACP domain, module 12
6454	6873	KS13	KS domain, module 13

(xiii) SEQ ID No.: 37
Translation Product Name: NysI

Start	End	Name	Description
34	448	KS9	KS domain, module 9
572	890	AT9	AT domain, module 9
904	1123	DH9	DH domain, module 9

1443	1686	KR9	KR domain, module 9
1720	1793	ACP9	ACP domain, module 9
1813	2236	KS10	KS domain, module 10
2346	2664	AT10	AT domain, module 10
2678	2890	DH10	inactive DH domain, module 10
2983	3229	KR10	KR domain, module 10
3266	3336	ACP10	ACP domain, module 10
3355	3777	KS11	KS domain, module 11
3898	4217	AT11	AT domain (methylmalony-CoA-specific), module 11
4231	4432	DH11	inactive DH domain, module 11
4523	4769	KR11	KR domain, module 11
4806	4879	ACP11	ACP domain, module 11
4901	5325	KS12	KS domain, module 12
5432	5754	AT12	AT domain, module 12
5768	5977	DH12	inactive DH domain, module 12
6068	6315	KR12	KR domain, module 12
6348	6421	ACP12	ACP domain, module 12
6454	6873	KS13	KS domain, module 13
6973	7293	AT13	AT domain, module 13
7307	7448	DH13	inactive DH domain, module 13
7535	7774	KR13	inactive KR domain, module 13
7813	7886	ACP13	ACP domain, module 13
7908	8323	KS14	KS domain, module 14
8430	8741	AT14	AT domain, module 14
8755	8962	DH14	inactive DH domain, module 14
9050	9296	KR14	KR domain, module 14
9319	9394	ACP14	ACP domain, module 14

(xiii) SEQ ID No.: 38

Translation Product Name: NysJ

Start	End	Name	Description
41	464	KS15	KS domain, module 15
578	889	AT15	AT domain, module 15

903	1102	DH15	DH domain, module 15
1446	1731	ER15	ER domain, module 15
1740	1988	KR15	KR domain, module 15
2023	2096	ACP15	ACP domain, module 15
2117	2538	KS16	KS domain, module 16
2635	2953	AT16	AT domain, module 16
2967	3167	DH16	inactive DH domain, module 16
3257	3500	KR16	KR domain, module 16
3539	3612	ACP16	ACP domain, module 16
3634	4057	KS17	KS domain, module 17
4153	4472	AT17	AT domain, module 17
4486	4725	DH17	inactive DH domain, module 17
4997	5245	KR17	KR domain, module 17
5277	5350	ACP17	ACP domain, module 17

(xiii) SEQ ID No.: 39

Translation Product Name: NysK

Start	End	Name	Description
34	457	KS18	KS domain, module 18
568	881	AT18	AT domain, module 18
898	1102	DH18	inactive DH domain, module 18
1416	1663	KR18	KR domain, module 18
1695	1769	ACP18	ACP domain, module 18
1849	2066	TE	thioesterase domain

(xiv) SEQ ID No.: 43

Translation Product Name: NysRIV (long)

Start	End	Name	Description
31	85	PAS	PAS-like domain
113	120	P-loop	ATP/GTP binding site motif A
165	193	HTH	LuxR helix-turn-helix motif (DNA binding)

As referred to in the above "inactive" denotes DH domains which lack the conserved amino acid sequence representing the active site motif $H(X_3)G(X_4)P$ found in DH in other PKSs. It will however be appreciated that these domains may have activity although this is likely to be distinct from the activity of DH domains in other PKSs.

It will be seen that SEQ ID Nos. 5 (NysA), 6 (NysB), 7 (NysC), 20 and 37 (NysI), 38 (NysJ) and 39 (NysK) constitute actual "PKS" enzymes, namely enzymes involved in polyketide synthesis. These gene products contain identifiable enzymatic domains and modules which are tabulated in Table 2 above and shown also in Figures 4, 8 and 9 (see also Example 1 and Table 4, and Example 4 below which describes the DNA sequence analysis of nystatin biosynthesis gene cluster in more detail). Such individual domains and molecules, as identified herein form separate aspects of the present invention.

SEQ ID NOs 3 and 26 (NysDII), 4 (NysDI), 8 (NysE), 16 (NysF), 19 (NysDIII), 40 (NysL), 41 (NysM) and 42 (NysN) represent other enzymes functional in polyketide or macrolide synthesis e.g. in polyketide release from PKS, post-translational PKS modification, and polyketide modification. SEQ ID NOs 10 to 15 and 43 (NysRI to NysRV, and ORF2) respectively represent transcriptional regulators, and SEQ ID NOs 17 and 18 (NysG and NysH) represent transport proteins which are presumed to be involved in polyketide transport from the cell. This is also described in more detail in the Examples below. Such functional proteins represent separate aspects of the present invention. Also included are functional parts or fragments of such proteins i.e. active parts or fragments which retain (i.e. exhibit measurable levels of) the biological activity of the parent molecule from which they are derived (i.e. of the whole protein or polypeptide).

The nucleotide sequences of the present invention

provide important tools and information which can be utilised in a number of ways to manipulate nystatin biosynthesis, to synthesise new nystatin derivatives or novel polyketide or macrolide structures, and to provide novel or modified PKS systems (by "PKS system" here is meant a polyketide synthesis system i.e. a gene cluster or protein complex, collection or assembly, which is functional in polyketide synthesis, but which is not necessarily restricted to PKS enzymes or enzymatic domains, and which may contain also other functional activities, e.g. other enzymatic (e.g. modificatory) or transporter or regulatory functional proteins).

Thus, for example, the entire nystatin PKS gene cluster or PKS synthetic system as provided herein, or a portion thereof, may be subjected to modification so as to modify one or more genes, or one or more modules, or enzymatic domains, or functional sequences within it. Such modified or derivatised PKS systems may be used to synthesize novel or modified polyketide moieties, as will be described in more detail below. In this situation, the nystatin PKS system provided herein, or a fragment or portion thereof, may function as an "origin" or "template" or "source" system or sequence for modification.

More particularly, in one such embodiment and as further described below, the non-functional parts (e.g. non-biologically active parts) of said system may be utilised as a "scaffold", and the functional parts (e.g. sequences encoding enzymatic portions) may be modified to yield the derivative or modified PKS system. In some embodiments only a single selected, or few selected functional (e.g. enzymatic) regions may be modified, leaving the remaining sequence or structure largely intact.

Alternatively, the functional portions may be utilised as tools or materials for the modification of other "scaffold" structures e.g. individual nystatin

genes, modules or domains may be used for introduction (e.g. insertion or replacement) into other PKS scaffold structures e.g. PKS scaffold systems derived from PKS systems for other macrolide antibiotics e.g. erythromycin, rapamycin etc.

Included within the scope of the invention are synthetic or recombinant polyketide synthase enzymes derived from the scaffold encoded by the nystatin gene cluster which are modified to include one or more functional units derived from other modular enzymes. Such functional units may encode a catalytic or transport protein domain for example a ketoreductase domain from a PKS enzyme or an ACP domain from a modular hybrid polyketide/peptide synthesising enzyme. Such domains can be derived from enzyme domain DNA sequences from, for example, polyketide synthesising enzymes, peptide synthesising enzymes, hybrid peptide polyketide synthesising enzymes, fatty acid synthesising enzymes or other enzyme domains known in the art. Analogously, there are included within the scope of the invention, synthetic or recombinant polyketide synthase enzymes derived from the scaffold encoded by a different polyketide synthase gene cluster, or modular enzyme encoding gene cluster, which are modified to include one or more functional units derived from the nystatin gene cluster.

Thus, the sequence and activity information provided here for the nystatin biosynthesis gene cluster may be used to alter existing known gene clusters and hence the products they produce. In particular, selection and incorporation of particular domains described herein (or modification of existing sequences) into existing PKS gene clusters will allow incorporation of particular properties attributable to the nystatin gene cluster.

Thus, in a very general sense, the present invention provides the use of the nucleic acid molecules

of the invention as defined herein in the preparation of a modified PKS system, or in the preparation of modified polyketide molecules.

Such novel or modified polyketide or macrolide molecules form a separate aspect of the present invention.

The nucleotide sequences may be utilised in this way according to the present invention in a random or directed or designed manner, e.g. to obtain and test a particular predetermined or pre-designed structure, or to create random molecules, for example libraries of polyketide structures, e.g. for screening (this is also described in more detail below).

Whether for modification within the nystatin-PKS scaffold, or for introduction into an alternative scaffold structure, the genes or genetic elements which can be modified include not only the actual PKS genes (which encode NysA, NysB, NysC, NysI, NysJ and NysK) or the individual molecules or domains thereof, but also genes encoding other enzymes or functional proteins involved in nystatin biosynthesis and transport (referred to herein collectively as "PKS genes" or "nystatin genes").

As regards the actual PKS genes, as will be described in more detail below, these may be modified to change the nature of the loading domain molecule which determines the nature of the starter unit, the number of modules, the nature of the extender, as well as the various dehydratase, reductase and synthase activities which determine the structure of the polyketide chain.

Other genes which can be modified include the thioesterase gene, (encoding NysE; SEQ ID NO. 8), which may be modified to increase the efficiency of the PKS system (in the case of a thioesterase having "editing" activity which clears the inappropriate substrates from the PKS). If the thioesterase simply cleaves the final product off the PKS, it can be used for making nystatin

derivatives with a smaller macrolactone ring by truncating nystatin PKS, and fusing this thioesterase to the end of the truncated protein via genetic engineering.

Regulatory genes: activators can be overexpressed and repressors inactivated in order to boost polyketide or antibiotic production. This may be of particular importance for the production of new nystatin derivatives in recombinant strains, (which may be produced in very small quantities).

The putative 4'-phosphopantetheine (PPT) transferase gene (encoding NysF; SEQ ID NO: 16) can be overexpressed in order to achieve efficient post-translational modification and full functionality of the PKS. It can also be used for expression of the nystatin (or other) PKS in a heterologous host, which lacks the specific PPT activity. Such hosts may include *E.coli*, *Saccharomyces cereviseae*, etc.

Deoxysugar genes: glycosyltransferase (encoding NysDI; SEQ ID NO:4) can be overexpressed in order to boost glycosylation of the synthesised molecules e.g. novel nystatin derivatives. It can also be modified by *in vitro* mutagenesis in order to increase its specificity towards the new substrates. Inactivation of this glycosylstranferase will result in a recombinant strain producing non-glycosylated nystatin (probably also lacking some modifications) which can be used, for example, for chemical modifications, or enzymatic assays for screening new modification activities.

Aminotransferase (NysDII; SEQ ID Nos: 3 and 36) may be inactivated to give a nystatin derivative. This enzyme is presumed to attach the amino group on the deoxysugar mycosamine. This gene may also be expressed in other streptomycetes in order to achieve the same reaction with another deoxysugar normally lacking an amino group.

ABC transporters (e.g. NysH and NysG; SEQ ID NOs 17

and 18): can be overexpressed in order to make the efflux of nystatin and its derivatives more efficient. They may also be mutated in order to shift their specificity towards different compounds. They may be inactivated, if it is desired for any reason to accumulate the nystatin or its derivatives inside the cell.

The genes encoding monooxygenases NysL and NysN (SEQ ID Nos. 40 and 42) can be inactivated in *S. noursei* in order to obtain non-hydroxylated and non-oxidized nystatin derivatives. Alternatively, they can be mutated with the aim of changing their specificities toward nystatin precursors. Overexpression of *nys*L and *nys*N may potentially lead to increased yield of nystatin or its derivatives if the hydroxylation and/or oxidation steps are limiting in the nystatin biosynthetic pathway. Genetic manipulations with *nys*M encoding ferredoxin (SEQ ID No.41) might also be useful if one wishes to establish an *in vitro* P450 hydroxylase system for modifications of nystatin precursors.

Thus, in addition to modification of the nystatin PKS system, or modification of other PKS systems by using the "nystatin" genes, the nucleic acid molecules of the invention can also be utilised to manipulate or facilitate the biosynthetic process, for example by extending the host range or increasing yield or production efficiency etc.

In order to enable practice of the invention according to the principles above, the invention also provides an expression vector, and host cells containing a nucleic acid molecule as herein defined.

Also provided are methods for production of a polyketide or macrolide molecule (e.g. nystatin or a nystatin derivative), comprising expressing within a host cell, a nucleic acid molecule as defined above. The polyketide or macrolide molecule produced within the host cell or secreted or exported by the host-cell as a

result of expression of the nucleic acid molecule (i.e. expression of the introduced "PKS synthesis machinery") may then be recovered.

This method of the invention may thus involve growing or cultivating the host cell under conditions whereby the nucleic acid molecule is expressed, and allowing the expression product(s) of the nucleic acid molecule to synthesise the polyketide/macrolide molecule, or in other words, growing or cultivating the host cell under conditions wherein the polyketide or macrolide is produced.

Also provided are methods for preparing recombinant nucleic acid molecules according to the invention, comprising inserting the nucleic acid molecules containing the nucleotide sequences of the invention into another nucleic acid molecule, e.g. into vector nucleic acid, e.g. vector DNA.

Expression vectors of the invention may include appropriate control sequences such as for example translational (e.g. start and stop codons, ribosomal binding sites) and transcriptional control elements (e.g. promoter-operator regions, termination stop sequences) linked in matching reading frame with the nucleic acid molecules of the invention.

Vectors according to the invention may include plasmids and viruses (including both bacteriophage and eukaryotic viruses) according to techniques well known and documented in the art, and may be expressed in a variety of different expression systems, also well known and documented in the art.

A variety of techniques are known and may be used to introduce such vectors into prokaryotic or eukaryotic cells for expression, or into germ line or somatic cells to form transgenic animals. Suitable transformation or transfection techniques are well described in the literature.

The invention also includes transformed or

transfected prokaryotic or eukaryotic host cells, for transgenic organisms containing a nucleic acid molecule according to the invention as defined above. Such host cells may for example include prokaryotic cells such as *E.coli, Streptomyces* and other bacteria, eukaryotic cells such as yeasts or the baculovirus-insect cell system, transformed mammalian cells and transgenic animals and plants.

The nucleic acid molecules contained in the expression vectors, and host cells and organisms etc. above may also be, as will be described in more detail below, derivative nucleic acid molecules, derived from the nucleic acid molecules defined above, either by modification or by introducing said molecules or parts thereof into, or combining with, other nucleic acid molecules.

Thus, in one aspect, the invention provides recombinant materials for the production of combinatorial libraries of polyketides wherein the polyketide members of the library are synthesized by modified PKS systems derived from the naturally occurring nystatin A1 system provided herein by using this system as a scaffold. Generally, many members of these libraries may themselves be novel compounds, and the invention further includes novel polyketide members of these libraries. The invention methods may thus be directed to the preparation of an individual polyketide. The polyketide may or may not be novel, but the method of preparation permits a more convenient method of preparing it. The resulting polyketides may be further modified to convert them to antibiotics, typically through glycosylation. The invention also includes methods to recover novel polyketides with desired binding activities by screening the libraries of the invention.

Thus, in one aspect, the invention is directed to a method of preparing a nucleic acid molecule which

contains or comprises a nucleotide sequence encoding a modified polyketide synthase enzyme or enzyme system. The method comprises using the nystatin PKS encoding sequence as provided herein as a scaffold and modifying the portions of the nucleotide sequence that encode enzymatic or other functional activities e.g. by mutagenesis, inactivation (e.g. by deletion or insertion), or replacement. The thus modified nucleotide sequence encoding a modified PKS can then be used to modify a suitable host cell and the cell thus modified employed to produce a polyketide different from that produced by the native nystatin PKS, whose scaffolding has been used to support modifications of enzymatic activity.

Alternatively, one or more portions of the nucleotide sequence that encode enzymatic or other functional activities may be introduced into an alternative (i.e. different "second") PKS scaffold (i.e. a scaffold derived from a further "second" PKS system, different from the nystatin PKS system).

The invention is also directed to polyketides thus produced and the antibiotics to which they may then be converted.

In another aspect, the invention is directed to a multiplicity of cell colonies comprising a library of colonies wherein each colony of the library contains an expression vector for the production of a different modular PKS, but derived from the nystatin PKS of the invention, as defined above. The library of different modular PKS may be obtained by modifying one or more of the regions of a naturally occurring "nystatin" gene or gene cluster encoding an enzymatic activity so as to alter that activity, leaving intact the scaffold portions of the naturally occurring gene.

In another aspect, the invention is directed to a multiplicity of cell colonies comprising a library of colonies wherein each colony of the library contains a

different modular PKS derived from the nystatin PKS of the invention. The invention is also directed to methods to produce libraries of PKS complexes and to produce libraries of polyketides by culturing these colonies, as well as to the libraries so produced. In addition, the invention is directed to methods to screen the resulting polyketide libraries and to novel polyketides contained therein.

As mentioned above, a structural and functional sequence analysis of the nystatin PKS gene cluster/system is presented in the Examples below and the DNA sequences are shown in SEQ ID NO 1, 2 and 35, and further analysed in Tables 1 and 2 above, SEQ ID NOs 3 to 20, and 36 to 42 and in Figures 2, 3, 7, 8 and 9. The modular and "domain" encoding structure of the "PKS" gene may be seen. A module may typically contain a ketosynthase (KS), an acyltransferase (AT) and an acyl carrier protein (ACP). These three functions are sufficient to activate an extender unit and attach it to the remainder of the growing molecule. Additional activities that may be included in a module relate to reactions other than the Claisen condensation, and include a dehydratase activity (DH), an enoylreductase activity (ER) and a ketoreductase activity (KR). The loading module catalyses the initial condensation, i.e. it begins with a "loading domain" represented by AT and ACP, which determine the nature of the starter unit. The "finishing" of the molecule is believed to be regulated by thioesterase activity (TE) and it is believed that this is achieved by the TE activity embedded in NysK. This thioesterase appears to catalyse cyclization of the macrolide ring thereby increasing the yield of the polyketide product. The NysE TE activity is believed to be an "editing" one, and participates in cleaving off certain substrates from the nystatin PKS complex.

It will be seen from the sequences, Figures and

Tables above and below, that the regions in the genes and modules that encode enzymatic activities are separated by linker or "scaffold"-encoding regions. These scaffold regions encode amino acid sequences that space the enzymatic/functional activities at the appropriate distances and in the correct order. Thus, these linker regions collectively can be considered to encode a "scaffold" into which the various activities are placed in a particular order and spatial arrangement. It should however be noted that in some instances regions of the scaffold may be deleted or modified without significantly affecting the activity of the resultant PKS. Indeed the sequence encoding some domains with functional activity may be fully or partially deleted without significant effects. Thus as used herein "scaffold" refers to portions of PKS cluster not directly attributable to functional e.g. enzymatic activities of said PKS, but responsible for maintenance of its overall activity, e.g. providing correct spatial orientation or structure. Said scaffold may comprise all linker and non-functional regions of the PKS or a functionally active (i.e. retaining structural integrity) part thereof. This organization is similar in other naturally occurring modular PKS gene clusters.

The invention provides libraries or individual modified forms, ultimately of polyketides, by generating modifications in the nystatin PKS gene cluster so that the protein complexes produced by the cluster have altered activities in one or more respects, and thus produce polyketides other than the natural product of the PKS (i.e. nystatin A1). Novel polyketides may thus be prepared, or polyketides in general prepared more readily, using this method. By providing a large number of different genes or gene clusters derived from the naturally occurring nystatin PKS gene cluster, each of which has been modified in a different way from the native cluster, an effectively combinatorial library of

polyketides can be produced as a result of the multiple variations in these activities. Alternatively the nystatin PKS "functional regions" (e.g. genes, modules or domains) may be used, for introduction into a "scaffold" obtained from another naturally occurring PKS system. The modified PKS encoding sequences and systems used in the present invention thus represent modular polyketide synthases "derived from" a naturally occurring nystatin PKS.

By a modular PKS "derived from" the nystatin PKS is meant a modular polyketide synthase (or its corresponding encoding gene(s)) that retains the scaffolding of all of the utilized portion of the naturally occurring gene. (Not all modules or genes need be included in the constructs). On the constant scaffold, at least one enzymatic or functional activity is mutated, deleted or replaced, so as to alter the activity. Alteration results when these activities are deleted or are replaced by a different version of the activity, or simply mutated in such a way that a polyketide other than the natural product results from these collective activities. This occurs because there has been a resulting alteration of the starter unit and/or extender unit, and/or stereochemistry, and/or chain length or cyclization and/or reductive or dehydration cycle outcome at a corresponding position in the product polyketide. Where a deleted activity is replaced, the origin of the replacement activity may come from a corresponding activity in a different naturally occurring polyketide synthase or from a different region of the same PKS. Alternatively, such a "derived" modular PKS may incorporate one or more enzymatic or other functional activities (or their encoding nucleotide sequences) obtained or derived from the nystatin PKS described herein, in the scaffolding of a second, different modular PKS (or its gene).

Modification or manipulation of the modular PKS may

involve truncation, e.g. gene or domain or module deletion or domain/gene/module swapping, addition or inactivation, which may involve insertion or deletion. Alternatively, random or directed modifications (i.e. mutations) may be made in the nucleotide sequence of the selected portion (e.g. in a gene/domain/module etc).

The derivative may contain preferably at least a thioesterase activity from the nystatin PKS gene cluster.

Advantageously, a polyketide synthase "derived from" the nystatin PKS may contain the scaffolding encoded by all or the portion employed of the nystatin synthase gene, contains at least two modules that are functional, preferably four or more modules and contains mutations, deletions, or replacements of one or more of the activities of these functional modules so that the nature of the resulting polyketide is altered. This definition applies both at the protein and genetic levels. Particular preferred embodiments include those wherein a KS, AT, KR, DH or ER has been inactivated or deleted or replaced by a version of the activity from a different PKS or from another location within the same PKS. Also preferred are derivatives where at least one noncondensation cycle enzymatic activity (KR, DH or ER) has been deleted or wherein any of these activities has been mutated so as to change the ultimate polyketide synthesized.

Thus, there are five degrees of freedom for constructing a polyketide synthase in terms of the polyketide that will be produced. First, the polyketide chain length will be determined by the number of modules in the PKS system. Second, the nature of the carbon skeleton of the PKS will be determined by the specificities of the acyl transferases which determine the nature of the extender units at each position -- e.g. malonyl, methyl malonyl, or ethyl malonyl, etc. Third, the loading domain specificity will also have an

effect on the resulting carbon skeleton of the polyketide. Thus, the loading domain may use a different starter unit, such as acetyl, propionyl, and the like. Fourth, the oxidation state at various positions of the polyketide will be determined by the dehydratase and reductase portions of the modules. This will determine the presence and location of ketone, alcohol, double bonds or single bonds in the polyketide.

Finally, the stereochemistry of the resulting polyketide is a function of three aspects of the synthase. The first aspect is related to the AT/KS specificity associated with substituted malonyls as extender units, which affects stereochemistry only when the reductive cycle is missing or when it contains only a ketoreductase since the dehydratase would abolish chirality. Second, the specificity of the ketoreductase will determine the chirality of any β-OH. Finally, the enoyl reductase specificity for substituted malonyls as extender units will influence the result when there is a complete KR/DH/ER available.

Thus, the modular nystatin PKS system permits a wide range of polyketides to be synthesized. As compared to the aromatic PKS systems, a wider range of starter units including aliphatic monomers (acetyl, propionyl, butyryl, isovaleryl, etc.), aromatics (aminohydroxybenzoyl), alicyclics (cyclohexanoyl), and heterocyclics (thiazolyl) are found in various macrocyclic polyketides. Recent studies have shown that modular PKSs have relaxed specificity for their starter units. Modular PKSs also exhibit considerable variety with regard to the choice of extender units in each condensation cycle. The degree of β-ketoreduction following a condensation reaction has also been shown to be altered by genetic manipulation (Donadio, S. et al. Proc. Natl. Acad. Sci. USA (1993) 90:7119-7123). Likewise, the size of the polyketide product can be varied by designing mutants with the appropriate number

of modules (Kao, C. M. et al. J. Am. Chem. Soc. (1994) 116: 11612-11613). Lastly, these enzymes are particularly well-known for generating an impressive range of asymmetric centres in their products in a highly controlled manner. The polyketides and antibiotics produced by the methods of the present invention are typically single stereoisomeric forms. Although the compounds of the invention can occur as mixtures of stereoisomers, it is more practical to generate individual stereoisomers using this system. Thus, the combinatorial potential within modular PKS pathways based on any naturally occurring modular, such as the nystatin, PKS scaffold is virtually unlimited.

In general, the polyketide products of the PKS must be further modified, typically by glycosylation, in order to exhibit antibiotic activity. Methods for glycosylating the polyketides are generally known in the art; the glycosylation may be effected intracellularly by providing the appropriate glycosylation enzymes or may be effected *in vitro* using chemical synthetic means.

The macrolide antibiotics, polyketide moieties of which are synthesised by modular PKSs, may contain any of a number of different deoxysugars. The nystatin molecule contains mycosamine deoxysugar moiety. Deoxysugar biosynthesis starts typically with glucose-1-phosphate and proceeds through the action of dTDP-glucose synthase and dTDP-glucose-4,6-dehydratase. The product of the latter, typically a dTDP-4,6-keto-6-deoxyglucose, is further subjected to at least two of the following reactions - epimerisation, isomerisation, reduction, dehydration, transamination, or methylation - to give a dTDP-D-deoxysugar. The latter is then attached to the macrolactone ring via the action of a glycosyltransferase, hence providing for the glycosylation of the macrolide compound.

Glycosylation can also be effected using the non-glycosylated macrolides as starting materials, and using

mutants of streptomycetes or other organisms (i.e. *Myxococcus*, *Pseudomonas*, *Mycobacterium* etc.) that can provide the glycosylation activities. Alternatively, glycosyltransferase-encoding genes from the organisms mentioned above can be introduced in *S. noursei* or other organisms containing the native or modified nystatin PKS genes or portions thereof in order to provide the desired glycosylation. The deoxysugar biosynthesis genes from the nystatin gene cluster can be used for complementation of corresponding activities in different PKS producers, as well as for engineering the biosynthetic pathways for alternative deoxysugars.

The derivatives of nystatin PKS can be prepared by manipulation of the relevant genes, or by introducing the nystatin genes or portions thereof into another PKS. A large number of modular PKS gene clusters have been mapped and/or sequenced, including erythromycin, soraphen A, rifamycin, avermectin and rapamycin, which have been completely mapped and sequenced, and FK506 and oleandomycin which have been partially sequenced, and candicidin, pimaricin and nemadectin which have been mapped and partially sequenced. Additional modular PKS gene clusters are expected to be available as time progresses. These genes can be manipulated using standard techniques to delete or inactivate activity encoding regions, insert regions of genes encoding corresponding activities from the same or different PKS systems, or otherwise mutate using standard procedures for obtaining genetic alterations. Of course, portions of, or all of, the desired derivative coding sequences can be synthesized using standard solid phase synthesis methods such as those described by Jaye et at., J. Biol. Chem. (1984) 259:6331, and which are available commercially from, for example, Applied Biosystems, Inc.

In order to obtain nucleotide sequences encoding a variety of derivatives of the naturally occurring PKS, and thus a variety of polyketides for construction of a

library, a desired number of constructs can be obtained by "mixing and matching" enzymatic activity-encoding portions, and mutations can be introduced into the native host (i.e. nystatin) PKS gene cluster or portions thereof.

Mutations can be made to the native sequences using conventional techniques. The substrates for mutation can be an entire cluster of genes or only one or two of them; the substrate for mutation may also be portions of one or more of these genes. Techniques for mutation are well known in the art and described in the literature, for example in WO98/49315 and the references cited therein. Such techniques include preparing synthetic oligonucleotides including the mutation(s) and inserting the mutated sequence into the gene encoding a PKS subunit using restriction endonuclease digestion. (See, e.g. Kunkel, T.A., Proc. Natl. Acad. Sci. USA (1985) 82:448; Geisselsoder et al. BioTechniques (1987) 5:786.) Alternatively, the mutations can be effected using a mismatched primer (generally 10-20 nucleotides in length) which hybridizes to the native nucleotide sequence, at a temperature below the melting temperature of the mismatched duplex. The primer can be made specific by keeping primer length and base composition within relatively narrow limits and by keeping the mutant base centrally located (Zoller and Smith, Methods Enzymol. (1983) 100:468). Primer extension is effected using DNA polymerase, the product cloned and clones containing the mutated DNA, derived by segregation of the primer extended strand, selected. Selection can be accomplished using the mutant primer as a hybridization probe. The technique is also applicable for generating multiple point mutations. See, e.g. Dalbie-McFarland et al. Proc. Natl. Acad. Sci. USA (1982) 79:6409. PCR mutagenesis will also find use for effecting the desired mutations.

Random mutagenesis of selected portions of the

nucleotide sequences encoding enzymatic activities can be accomplished by several different techniques known in the art, e.g. by inserting an oligonucleotide linker randomly into a plasmid, by irradiation with X-rays or ultraviolet light, by incorporating incorrect nucleotides during *in vitro* DNA synthesis, by error-prone PCR mutagenesis, by preparing synthetic mutants or by damaging plasmid DNA *in vitro* with chemicals. Chemical mutagens include, for example, sodium bisulfite, nitrous acid, nitrosoguanidine, hydroxylamine, agents which damage or remove bases thereby preventing normal base-pairing such as hydrazine or formic acid, analogues of nucleotide precursors such as 5-bromouracil, 2-aminopurine, or acridine intercalating agents such as proflavine, acriflavine, quinacrine, and the like. Generally, plasmid DNA or DNA fragments are treated with chemicals, transformed into *E. coli* and propagated as a pool or library of mutant plasmids.

In addition to providing mutated forms of regions encoding enzymatic or other functional activity, regions encoding the desired functions or activities may be recovered from different locations in the same nystatin PKS, for example, using PCR techniques with appropriate primers. By "corresponding" activity encoding regions is meant those regions encoding the same general type of activity -- e.g. a ketoreductase activity in one location of a gene cluster would "correspond" to a ketoreductase-encoding activity in another location in the gene cluster.

If replacement of a particular target region in a host polyketide synthase is to be made (be this host nystatin PKS, or a different PKS into which "nystatin" sequences are to be inserted), this replacement can be conducted *in vitro* using suitable restriction enzymes or can be effected *in vivo* using recombinant techniques involving homologous sequences framing the replacement

gene in a donor plasmid and a receptor region in a recipient plasmid, genome or chromosome. Such systems, advantageously involving plasmids of differing temperature sensitivities are described, for example, in PCT application WO 96/40968.

WO 00/77181 describes methods of assembling several DNA units in sequence into large DNA constructs which are applicable to the recombinant polyketide synthases within the scope of the invention.

The vectors used to perform the various operations to replace the enzymatic activity in the host PKS genes or to support mutations in these regions of the host PKS genes may be chosen to contain control sequences operably linked to the resulting coding sequences in a manner that expression of the coding sequences may be effected in a appropriate host. However, simple cloning vectors may be used as well.

If the cloning vectors employed to obtain PKS genes encoding derived PKS lack control sequences for expression operably linked to the encoding nucleotide sequences, the nucleotide sequences are inserted into appropriate expression vectors. This need not be done individually, but a pool of isolated encoding nucleotide sequences can be inserted into host vectors, the resulting vectors transformed or transfected into host cells and the resulting cells plated out into individual colonies.

Suitable control sequences include those which function in eucaryotic and prokaryotic host cells. Preferred hosts include prokaryotic hosts and fungal systems such as yeast, but single cell cultures of, for example, mammalian cells could also be used. There is no particular advantage, however, in using such systems. Particularly preferred are yeast and prokaryotic hosts which use control sequences compatible with *Streptomyces* spp. Suitable control sequences for single cell cultures of various types of organisms are well known in

the art. Systems for expression in yeast, including control sequences which effect secretion are widely available and are routinely used. Control elements include promoters, optionally containing operator sequences, and other elements depending on the nature of the host, such as ribosome binding sites. Particularly useful promoters for prokaryotic hosts include those from PKS gene clusters which result in the production of polyketides as secondary metabolites, including those from aromatic (Type II) PKS gene clusters. Examples are *act* promoters, *tcm* promoters, spiramycin promoters, and the like. However, other bacterial promoters, such as those derived from sugar metabolizing enzymes, such as galactose, lactose (tac) and maltose, are also useful. Additional examples include promoters derived from genes encoding biosynthetic enzymes such as tryptophan synthase (trp), the β-lactamase (bla), bacteriophage lambda FL, T5 and T7. In addition, synthetic promoters, such as the tac promoter (U.S. Patent No. 4,551,433), can be used.

Other regulatory sequences may also be desirable which allow for regulation of expression of the PKS replacement sequences relative to the growth of the host cell. Regulatory sequences are known to those of skill in the art, and examples include those which cause the expression of a gene to be turned on or off in response to a chemical or physical stimulus, including the presence of a regulatory compound. Other types of regulatory elements may also be present in the vector, for example, enhancer sequences.

Selectable markers can also be included in the recombinant expression vectors. A variety of markers are known which are useful in selecting for transformed cell lines and generally comprise a gene whose expression confers a selectable phenotype on transformed cells when the cells are grown in an appropriate selective medium. Such markers include, for example,

genes which confer antibiotic resistance or sensitivity to the plasmid. Alternatively, several polyketides are naturally coloured and this characteristic provides a built-in marker for screening cells successfully transformed by the present constructs.

The various PKS nucleotide sequences, or a mixture of such sequences, can be cloned into one or more recombinant vectors as individual cassettes, with separate control elements, or under the control of, e.g. a single promoter. The PKS subunits or mixture of components can include flanking restriction sites to allow for the easy deletion and insertion of other PKS subunits or mixture components so that hybrid PKSs can be generated. The design of such unique restriction sites is known to those of skill in the art and can be accomplished using the techniques described above, such as site-directed mutagenesis and PCR.

As described above, particularly useful control sequences are those which themselves, or using suitable regulatory systems, activate expression during transition from growth to stationary phase in the vegetative mycelium. The system contained in plasmid RM5, i.e. the *actI*/*actIII* promoter pair and the *actII*-ORF4, an activator gene, is particularly preferred (McDaniel et al., Science, v. 262, p 1546-1550, 1993). Particularly preferred hosts are those which lack their own means for producing polyketides so that a cleaner result is obtained. Illustrative host cells of this type include the modified *S. coeticotor* CH999 culture described in PCT application WO 96/40968 and similar strains of *S. lividans*.

The expression vectors containing nucleotide sequences encoding a modified PKS system or a variety of PKS systems for the production of different polyketides may then be transformed into the appropriate host cells, e.g. to construct a library. In one straightforward approach, a mixture of such vectors is transformed into

the selected host cells and the resulting cells plated into individual colonies and selected for successful transformants. Each individual colony will then represent a colony with the ability to produce a particular PKS synthase and ultimately a particular polyketide. Typically, there will be duplications in some of the colonies; the subset of the transformed colonies that contains a different PKS in each member colony can be considered the library. Alternatively, the expression vectors can be used individually to transform hosts, which transformed hosts are then assembled into a library. A variety of strategies might be devised to obtain a multiplicity of colonies each containing a PKS gene cluster derived from the nystatin host gene cluster so that each colony in the library produces a different PKS and ultimately a different polyketide. The number of different polyketides that are produced by the library is typically at least three (e.g. 2 mutations in the PKS genes which may appear separately or in combination), more typically at least ten, and preferably at least 20, more preferably at least 50, reflecting similar numbers of different altered PKS gene clusters and PKS gene products. The number of members in the library is arbitrarily chosen; however, the degrees of freedom outlined above with respect to the variation of starter, extender units, stereochemistry, oxidation state, and chain length is quite large.

Methods for introducing the recombinant vectors of the present invention into suitable hosts are known to those of skill in the art and typically include the use of $CaCl_2$ or other agents, such as divalent cations, lipofection, conjugation, protoplast transformation and electroporation.

A wide variety of hosts can be used, even though some hosts natively do not contain the appropriate post-translational mechanisms to activate the acyl carrier

proteins of the synthases. These hosts can be complemented with the appropriate recombinant enzymes, for example NysF, to effect these modifications.

The polyketide producing colonies can be identified and isolated using known techniques and the produced polyketides further characterized. The polyketides produced by these colonies can be used collectively in a panel to represent a library or may be assessed individually for activity.

The libraries can thus be considered at four levels: (1) a multiplicity of colonies each with a different PKS encoding sequence comprising a different PKS cluster but all derived from the nystatin PKS cluster; (2) colonies which contain the proteins that are members of the PKS produced by the coding sequences; (3) the polyketides produced; and (4) antibiotics derived from the polyketides.

Colonies in the library can be induced to produce the relevant synthases and thus to produce the relevant polyketides to obtain a library of candidate polyketides. The polyketides produced can be screened for antimicrobial, antitumour, antihelmintic or immunosuppressive activities, as well as for binding to desired targets, such as receptors, signalling proteins, and the like. The supernatants or culture pellets per se can be used for screening, or partial or complete purification of the polyketides can first be effected. Typically, such screening methods involve detecting the binding of each member of the library to receptor or other target ligand. Binding can be detected either directly or through a competition assay. Means to screen such libraries for binding are well known in the art.

Alternatively, individual polyketide members of the library can be tested against a desired target. In this event, screens wherein the biological response of the target is measured can more readily be included.

A large number of novel polyketides may be prepared according to the method of the invention, as illustrated by the representative in the Examples below. These novel polyketides may be useful intermediates in formation of compounds with antibiotic activity through glycosylation or reactions as described above. As indicated above, the individual polyketides may be reacted with suitable sugar derivatives to obtain compounds of antibiotic activity. Antibiotic activity can be verified using typical screening assays such as those set forth in Lehrer, R. et al., J. Immunol. Meth. (1991) 137:167-173.

Thus, in a further aspect, the invention provides a method of preparing a nucleic acid molecule comprising a nucleotide sequence encoding a modified nystatin PKS, wherein said modified nystatin PKS is derived from a nystatin PKS as defined herein (i.e. a naturally occurring nystatin PKS) encoded by a nucleotide sequence as defined herein) containing first regions which encode enzymatic or other functional activities and second regions which encode scaffolding amino acid sequences, said method comprising

(a) modifying at least one said first region; or

(b) incorporating at least one said first region into a scaffolding-encoding second region from a different PKS-encoding nucleotide sequence.

As discussed above in relation to the nucleic acid molecules of the invention, the first region may be any part (e.g. encoding a domain or a module or a part thereof) of a nucleotide sequence of the invention (i.e. SEQ ID NO 1 or 2 or 35).

Also provided are (i) a method of preparing a modified nystatin PKS as defined above, said method comprising expressing a nucleic acid molecule prepared as defined above within a host cell (i.e. culturing or growing a host cell containing such a nucleic acid molecule) under conditions whereby the modified nystatin

PKS is expressed), and (ii) a modified nystatin PKS so produced or so obtainable.

New polyketides produced by such a modified PKS are also within the scope of the invention, as are new antibiotics which are generally the glycosylated forms of these polyketides although some have activity without glycosylation which may be due to different post-translation modifications such as hydroxylation or oxidation.

The invention will now be described in more detail in the following non-limiting Examples with reference to the drawings in which:

Figure 1 shows the structure of the polyene antifungal antibiotic nystatin A1;

Figure 2 presents physical and functional maps of the *E.coli - Streptomyces* shuttle vector pSOK101, pSOK201 and pSOK804 used in Examples 1, 2 and 3;

Figure 3 is a schematic representation showing two regions of the *S.noursei* ATCC11455 genome encoding the nystatin biosynthesis gene (corresponding to SEQ ID NOs 1 and 2). Overlapping recombinant phages containing the presented DNA sequences are shown over the regions drawings (see Example 1);

Figure 4 is a schematic representation showing the functional organisation of the nystatin PKS NysA (SEQ ID NO 5), NysB (SEQ ID NO 6), NysC (SEQ ID NO 7) and NysI (SEQ ID NO 20) and their roles in nystatin biosynthesis;

Figure 5 is a schematic representation showing genetic manipulations of the module 5 in NysC PKS leading to production of new polyene compounds by recombinant *S.noursei* strains (see Example 2);

Figure 6 shows the UV spectra (in DMSO) for nystatin and new polyene compounds S44 and S48 obtained from recombinant *S. noursei* strains with genetically altered NysC PKS (see Example 2);

Figure 7 is a schematic representation showing the region of the *S. noursei* ATC11455 genome encoding the

nystatin biosynthetic gene cluster (corresponding to SEQ ID No. 35). Gene organisation within the gene cluster is shown. The inserts from the overlapping recombinant phages encompassing the cloned region are shown above the physical/genetic map. The *nys* genes are designated with capital letters in *italic*, other ORFs are numbered;

Figure 8 is a representation showing a proposed model for nystatin biosynthesis in *S. noursei*; and

Figure 9 is a schematic representation showing the functional organisation of the nystatin PKS NysA (SEQ ID No. 5), NysB (SEQ ID No. 6), NysC (SEQ ID No. 7), NysI (SEQ ID No. 37), NysJ (SEQ ID No. 38) and NysK (SEQ ID No. 39) proteins. KS^S - ketosynthase with the Cys to Ser substitution in active site; KS - ketosynthase; AT - acetate-specific acyltransferase; mAT - propionate-specific acetyltransferase; DH - dehydratase; DHi - inactive dehydratase; ER - enoyl reductase; KR - detoreductase; KRi - inactive ketoreductase; ACP - acyl carrier protein.

Figure 10 shows compounds that can be theoretically produced from the following manipulations within the nystatin gene cluster

-insertion of ER domain into module 3 (1)
-insertion of ER domain into module 4 (2);
-simultaneous inactivation of the ER domain in module 5 and insertion of the ER domain into module 3 (3);
-simultaneous inactivation of the ER domain in module 5 and insertion of the ER domain into module 4 (4);
-simultaneous inactivation of the ER domain in module 5 and insertion of the ER domain into module 7 (5);
-simultaneous inactivation of the ER domain in module 5 and insertion of the ER domain into module 8 (6);
-simultaneous inactivation of the ER domain in module 5 and insertion of the ER domain into module 9 (7);
-simultaneous inactivation of the ER domain in module 5 and insertion of the ER domains into modules 8 and 9 (8);

-simultaneous inactivation of the ER domain in module 5 and insertion of the ER domains into modules 7 and 8 (9).

Figure 11 shows compounds that can be theoretically produced from the following manipulations within the nystatin gene cluster:
-replacement of methylmalonyl-specific acetyltransferase (AT) domain in module 11 of the nystatin PKS with malonyl-specific AT domain (10);
-replacement of malonyl-specific AT domain in module 12 with methylmalonyl-specific AT domain with simultaneous replacement of methylmalonyl-specific AT domain in module 11 with malonyl-specific AT domain (11);
-replacement of malonyl-specific AT domain in module 10 with methylmalonyl-specific AT domain with simultaneous replacement of methylmalonyl-specific AT domain in module 11 with malonyl-specific AT domain (12);
-inactivation of P450 monooxygenase-encoding genes nysL or nysN (whichever is found to be responsible for oxygenation of the methyl group at C-16 on the nystatin molecule) (13).

Figure 12 shows compounds that can be theoretically produced from the following manipulations within the nystatin gene cluster:
-inactivation of dehydratase (DH) domain in module 3 of the nystatin PKS (14);
-inactivation of DH domain in module 4 (15);
-inactivation of DH domain in module 3 with simultaneous inactivation of ER domain in module 5 (16);
-inactivation of DH domain in module 4 with simultaneous inactivation of ER domain in module 5 (17) ;
-inactivation of DH domain in module 7 with simultaneous inactivation of ER domain in module 5 (18);
-inactivation of DH domain in module 8 with simultaneous inactivation of ER domain in module 5 (19);
-inactivation of DH domain in module 9 with simultaneous inactivation of ER domain in module 5 (20).

Example 1 - Cloning of the nystatin biosynthesis gene cluster

Bacterial strains, plasmids and growth conditions

Bacterial strains and plasmids used in this study are listed in Table 3. New strains and plasmids developed in the course of this study are described herein and shown in Figure 3. *S.noursei* ATCC 11455 and its mutants were grown on solid ISP2 medium (Difco), and in liquid TSB medium (Oxoid). Intergeneric conjugation from *E.coli* ET12567 (pUZ8002) into *Streptomyces* strains was done as described in Flett *et al*, FEMS Microbial Lett., v. 155: 223-229, (1997), except for the "heat shock" time, which was reduced to 5 minutes. Apramycin (Fluka) at a concentration 50 mg/ml was used to select for the *S.noursei* transconjugants on solid medium. For inoculation of the *S.noursei* ATCC11455 transconjugants prior to total DNA isolation, liquid medium TSB supplemented with 20 μg/ml apramycin was used. *E.coli* strains were grown and transformed as described in Sambrook *et al*, Cold Spring Harbor Laboratory (1989). *E.coli* ET12567 (pUZ8002) was maintained on the media containing 20μg/ml chloramphenicol and 50 μg/ml kanamycin.

Table 3 - Bacterial strains, plasmids and phages used in this study

Strain, plasmid or phage	Properties	Source or reference
E.coli DH5α	general cloning host	Sambrook *et al*, 1989, supra
E.coli XL1-Blue MRA (P2)	host for the gene library	Stratagene
E.coli ET12567	strain for intergeneric conjugation	MacNeil *et al*, Gene, v. 111: 61-68, 1992
S.noursei ATCC 11455	wild type, nystatin producer	ATCC

pGEM3Zf(-)	ColE1 replicon, Ap^R, 3.2kb	Promega
pGEM72f(-)	ColE1 replicon, Ap^R, 3.0 kb	Promega
pGEM11Zf(-)	ColE1 replicon, Ap^R, 3.2kb	Promega
pUZ8002	RK2 derivative, Km^R, Tc^R	D.H.Figurski
pWHM3	ColE1+pIJ101 replicons, $Thio^R$, 7.2kb	Vara *et al*, J.Bacteriol v. 171: 5872-5881, 1989
pSET152	ColE1 replicon+øC31 int, *oriT*, Am^R, 5.5kb	Bierman *et al*, Gene, v. 116: 43-49, 1992
pSOK101	pWHM3 derivative in which the 3.1kb *Bam*HI/*Sph*I fragment was replaced with the 3.0 kb *Bam*HI/*Sph*I fragment from pSET152 containing ColEI, *oriT* and Am^R, 7.1kb	This work (see Figure 2)
pGM11	pSG5 replicon, Neo^R, 5.3kb	Wohlleben & Muth, In "Plasmids, a practical approach", Ed. Hardy, IRL Press, p 147-175, 1993
pSOK201	pGM11 derivative in which the 1.2 kb *Eco*RI/*Hin*dIII fragment was replaced with the 3.0 kb *Eco*RI/*Hin*dIII fragment from pSOK101 containing ColEI, *oriT* and Am^R, 7.1 kb	This work (see Figure 2)

DASHII	bacteriophage λ vector	Stratagene
pSOK804	ColEI replicon, Am^R, *OriT*, int_{WVB}, $AttP_{WVB}$	This work (see Figure 2) and Van Mellaert et al., Microbiol., v. 144:3351-3358, 1998
pGEM7ermELi	pGEM7ZF plasmid containing PermE* promoter	C.R. Hutchinson

Am-apramycin, Ap-ampicilli, Neo-neomycin, Thio-thiostrepton, Km-kanamycin, Tc-tetracycline

Analysis of the secondary metabolite production

Fermentations were performed in Applicon 3-1 fermenters containing initially 1.3 1 SAO-23 medium containing (gl^{-1}):glucose·H_2O, 90; NH_4NO_3, 2.5; corn flour, 3.0; $MgSO_4 \cdot 7H_2O$, 0.4; KH_2PO_4,02; $CaCO_3$, 7; trace element solution, 3ml. Trace element solution (gl^{-1}):$FeSO_4.7H_2O$, 5.0; $CuSO_4.5H_2O$, 0.39; $ZnSO_4 7H_2O$, 0.44; $MnSO_4H_2O$, 0.15; $Na_2MoO_4.2H_2O$, 0.01; $CoCl_2.6H_2O$, 0.02; HCl, 50. The fermentations were performed at 28°C with pH controlled at 6.5-7.0 by HCl (2M) and NaOH (2M). The dissolved oxygen was controlled at >40% of saturation by the agitation (300-900 rpm) and aeration (0.25 vvm). Inocula for the fermentations (3 vol-%) with SAO-23 medium were grown in TSB-medium (TSB, Oxoid CM129, 37 gl^{-1}) at 28°C in shake flasks (500-ml baffled Erlenmeyer flasks with 100 ml medium; 200 rpm). Each shake flask was inoculated with 0.2 ml spore suspension and incubated for 18-20 hours. Nystatin production was assayed by HPLC of the dimethylformamide extracts of the cultures after fermentations (Raatikainen, J. Chromatogr., v. 588, 356-360, (1991)).

DNA Manipulation

Plasmid, phage and total DNA preparations, endonuclease digestions, ligations and fractionation were performed as described previously (Sambrook *et al.*, 1989, supra; Hopwood *et al*, 1985, supra). DNA fragments were isolated from agarose gels using the QIAGEN Kit (QIAGEN GmbH), labelled with the use of the digoxygenin kit from Boehringer Mannheim and used for Southern blot analysis according to the manufacturer's manual. DNA sequencing was performed at QIAGEN GmbH (Germany), and the data were analysed with the GCG software (Devereux *et al*, Nucleic Acids Res. v. 12: 387-395, 1984).

PCR-assisted amplification and cloning of a PKS-encoding DNA fragment from the S.noursei ATCC11455 genome

In order to obtain the DNA encoding the nystatin biosynthesis genes, the *S.noursei* ATCC1455 gene library was probed with labelled PKS-encoding DNA. To obtain the DNA probe, degenerate oligonucleotide primers were designed, which correspond to conserved amino acid regions within β-ketoacyl synthase (KS) and acyl carrier protein (ACP) domains of known modular PKSs. The degenerate primers used for amplification corresponded to the conserved amino acid motifs in ACP and KS domains in known PKS, and were designed according to the codon usage table for *Streptomyces* (Wright & Bibb, Gene, v. 113: 55-65, 1992). The ACP nucleotide primer (sense) corresponded to the motif Glu(Asp)Leu Gly Phe(Leu, Val) Asp Ser Leu (SEQ ID NO:21) and had the sequence 5' - GAG/C CTG/C GGC/G T/CTG/C GAC TCC/G CTG/C-3 (SEQ ID NO: 22). The KS nucleotide primer (antisense) corresponded to the motif Val Asp Thr Ala Cys Ser Ser (SEQ ID NO: 23) and had the sequence 5' - G/CGA G/CGA G/ACA/ G/CGC C/GGT GTC G/CAC-3' (SEQ ID NO: 24). Total DNA isolated from the *S.noursei* ATCC11455 was used as a template for polymerase chain reaction (PCR)-assisted amplification of the DNA fragment from the genome of this organism

with the use of KS and ACP oligonucleotide primers. From the relative position of the motifs on the modular PKSs it was assumed that resulting PCR product would be approx 0.7 kb in size. The 50μl PCR mixture contained 0.1 μg of *S.noursei* ATCC11455 total DNA, 25 pm of each ACP and KS oligonucleotide primers dNTPs (final concentration 350 μm), 1xPCR buffer from Expand High Fidelity PCR System (Boehringer Mannheim), and 1.5 U of the DNA polymerase mixture from the same system. The PCR was performed on the Perkin Elmer GeneAmp PCR System 2400 with the following program: 1 cycle of denaturation at 96°C (4 min), 35 cycles of denaturation/annealing/ synthesis at 94°C (45 sec) and 70°C (5 min) and 1 cycle of final annealing/extension at 72°C (7 min). The 0.7 kb DNA fragment obtained with this procedure was cloned in pUC18 vector in *E.coli* DH5α with the use of Sure Clone Ligation Kit (Pharmacia). One of the resulting recombinant plasmids, pPKS72 of 3.5kb, was subjected to DNA sequence analysis.

Subsequent cloning in *Escherichia coli* vector pUC18 and DNA sequencing of the resulting 0.7 kb PCR product, followed by conceptual translation and database search, confirmed that it encodes part of PKS type I. This DNA fragment was used as a probe for screening a *S.noursei* ATCC11455 gene library constructed in the phage vector DASHIII (see below) and one recombinant phage, designated lambda DASHII-N1, which hybridized to the probe, was isolated. As described further below, DASHII-N1 was used to generate further probes.

Construction and screening of the S.noursei ATCC1455 gene library

The *S.noursei* ATCC11455 gene library was constructed in phage lambda vector DASHII (Stratagene) according to manufacturer's instructions. Total DNA from *S.noursei* ATCC11455 was isolated as described in Hopwood *et al* (1985) supra, partially digested with *Sau*3

AI restriction enzyme and fractionated on the sucrose gradient as described in Sambrook *et al* (1989), supra. The fractions of *S.noursei* ATCC1455 DNA containing fragments of 13-17 kb in size were used for ligation with the DASHII vector arms digested with *Bam*HI restriction enzyme. *E.coli* XL1-Blue MRA (P2) (Stratagene) was used as a host for a gene library construction and propagation.

DNA fragments to be used as probes for screening the gene library were purified from agarose gels using QIAGEN Kit (QIAGEN GmbH, Germany), and labelled by the use of the digoxygenin (DIG) kit from Boehringer Mannheim (Germany), according to the manufacturer's instructions. Probes used for the library screening and relevant recombinant phages discovered:

Probe	DASHII recombinant phages found using this probe
PKS72	N1, N14
E12.1: from N1	N41, N42, N44, N45, N48
E4.7.2: from N1	N58
L42E9.1: from N42	N64, N76
B1.0_58: from N58	N69

Description of the probes:

1. PKS72 probe. The 0.7kb DNA fragment isolated from the pPKS72 plasmid (see above) with restriction enzymes *Eco*RI and *Hin*dIII was used as a PKS72 probe.

2. E12.1 probe. The 2.6 kb *Bam*HI fragment from the insert of recombinant phage N1, representing its left flanking region, was subcloned into pGEM3Zf(-), resulting in plasmid pGEM(B2.6)-1. This plasmid was digested with *Eco*RI/*Ava*I, and the 0.55 kb fragment corresponding to the left end of the N1 DNA insert was purified and used as E12.1 probe.

3. E4.7.2 probe. The 4.7 kb *Eco*RI fragment from the

recombinant phage N1, representing its right flanking region was subcloned into pGEM3Zf(-), resulting in plasmid pGEM (E4.7)-1. This plasmid was digested with *Eco*RI/*Hin*dIII, and the 1.5kb DNA fragment corresponding to the right end of the N1 DNA insert was purified and named E4.7.2.

4. L42E9.1 probe. The 9.0 kb *Eco*RI fragment representing the left flanking region of the DNA insert in the recombinant phage N42 was subcloned into pGEM3Zf(-), resulting in plasmid pH42E9.1. This plasmid was digested with *Eco*RI/*Bam*HI, and the 0.6 kb fragment corresponding to the left flank of the N42 DNA insert was purified and used as L42E9.1 probe.

5. L58B1.0 probe. The 3.0 kb *Eco*RI fragment representing the right flanking region of the recombinant phage N58 DNA insert was subcloned into pGEM3Zf(-), resulting in plasmid pGEM(E3.0)-58. From the latter plasmid, the 1.0 kb *Bam*HI fragment which is located on the right end of the N58 DNA insert was purified and used as L58B1.0 probe.

Gene disruption experiment with the nystatin biosynthesis gene cluster

A 4.2 kb *Bam*HI DNA fragment isolated from the DASHII-N1 recombinant phage was first cloned into the pGEM3Zf(-) vector in *E.coli*, resulting in the plasmid pGEM 4.2-1. DNA sequences on both ends of the cloned fragment were determined and, after database search, were found to encode PKS type I. The *S.noursei* DNA fragment cloned in pGEM4.2-1 was excised from this plasmid with restriction enzymes *Eco*RI and *Hin*dIII, and ligated with the 3.0 kb *Eco*RI/*Hin*dIII fragment from the vector pSOK201 (see Table 3 and Figure 3), and transformed into *E.coli*. Plasmid DNA designated pKO(4.2)-1 was recovered from transformants, and then was transferred into *S.noursei* ATCC1455 by conjugation as described in Example 1 under "Bacterial strains,

plasmids and growth conditions".

Since pKO(4.2)-1 is not capable of replicating in *S.noursei* ATCC11455, it was assumed that it will function as a suicide vector integrating into the genome of *S.noursei* via homologous recombination. As a result of such recombination, a PKS gene in the *S.noursei* ATCC11455 genome, for which 4.2 kb *Bam*HI fragment cloned in pKO(4.2)-1 was presumed to be internal, would have been inactivated by disruption of its coding region. Integration of pKO(4.2)-1 into the genome of the three *S.noursei* transconjugants was confirmed by Southern blot analysis with the use of labelled 4.2 kb *Bam*HI fragment from pGEM4.2-1 as a probe. One of the *S. noursei* disruption mutants carrying pKO(4.2)-1 integrated into its genome was tested for nystatin production in parallel with the parental strain ATCC11455 (see above for methods under "analysis of secondary metabolite production". While the latter was shown to produce nystatin at the expected level, no nystatin production was detected in the pKO(4.2)-1 disruption mutant, thus confirming the requirement of the identified PKS for nystatin biosynthesis.

Cloning of the nystatin biosynthesis gene cluster

In order to clone the entire gene cluster for the nystatin biosynthesis, the DNA fragments derived from the ends of the *S. noursei* DNA insert in the recombinant phage DASHII-N1 (N1), and subsequently found overlapping recombinant phages, were used as probes for screening the gene library (see above for probes). This screen resulted in isolation of the recombinant phages N14, N41, N42, N44, N45, N48, N58, N64, N69, and N76 comprising two regions (SEQ ID NOs 1 and 2 respectively) of the *S. noursei* ATCC11455 genome (approx. 98 kb total), as depicted in Fig. 4. A gene disruption experiment with the 4.3 kb *Eco*RI/*Bam*HI DNA fragment derived from the recombinant phage N64 (performed

essentially the same way as described above), confirmed that the second region (SEQ ID NO. 2) also encodes nystatin biosynthesis genes.

DNA sequence analysis of the nystatin biosynthesis gene cluster

The complete DNA inserts from recombinant phages mentioned above were subcloned either as *Xba*I or *Eco*RI fragments into pGEM3Zf(-) vector in an *E. coli* host, and nucleotide sequences were determined on both DNA strands of these fragments. Computer-assisted analysis of the DNA sequences comprising the two regions of the nystatin biosynthesis gene cluster (SEQ ID NOs 1 and 2 respectively) resulted in identification of the genes shown on Fig. 4 and listed in Table 4.

Table 4. Genes identified within the nystatin biosynthesis gene cluster of *S.noursei*

Designation	Product	Putative function
nysR1	transcriptional activator	regulation of nystatin production
nysR2	transcriptional activator	regulation of nystatin production
nysR3	transcriptional activator	regulation of nystatin production
nysR4	transcriptional activator	regulation
nysR5	transcriptional repressor	regulation
ORF1	peptidase	peptide metabolism
ORF2	transcriptional activator	regulation
nysA	PKS type I	nystatin polyketide backbone synthesis (loading module)
nysB	PKS type I	nystatin polyketide backbone synthesis (modules 1&2)

nysC	PKS type I	nystatin polyketide backbone synthesis (modules 3-8)
nysI (incomplete)	PKS type I	nystatin polyketide backbone synthesis (modules 9-13)
nysE	thioesterase	release of final product from PKS
nysD1	glycosyltransferase	attachment of mycosamine to the polyketide backbone
nysD2	aminotransferase	mycosamine biosynthesis
nysD3	GDP-mannose-4,6-dehydratase	mycosamine biosynthesis
nysH	ABC transporter	efflux of nystatin
nysG	ABC transporter	efflux of nystatin
nysF	4'-phosphopantetheine transferase	post-translational modification of PKS

Three complete (*nysA, nysB and nysC*) (in SEQ ID NO:1), and one incomplete (*nysI*) genes (in SEQ ID NO:2) encoding the PKSs type I were identified. The amino acid (aa) sequences of the products encoded by these four genes were analysed by comparison to the aa sequences of known PKSs type I (see also Table 2 above for molecule features). Since all four proteins displayed high degree of homology towards rifamycin and rapamycin PKSs (Aparicio et al., Gene, v. 169: 9-16, 1996; Tang et al., Gene, v. 216: 255-265, 1998), presumptive functional analysis of nystatin PKSs was based on comparison to the formers. The NysA protein of 1366 aa encodes one module of PKS composed of KS^S, AT, DH, KR, and ACP domains. The lack of a conserved cysteine residue in KS^S domain suggests that this module cannot perform condensation reaction, and thus most probably represents a loading module providing the acetate starter unit for initiation of nystatin

polyketide backbone biosynthesis (Bisang et al., Nature, v. 401: 502-505, 1999). Analysis of the 3192 aa sequence of NysB revealed that it contains two modules with KS, AT, KR, ACP, and apparently inactive DH domains. The AT domains identified in both NysB modules display features characteristic for the methylmalonylCoA-specific AT domains (Haydock et al., *FEBS Lett.*, v. 374: 246-248, 1995). This feature of the NysB protein suggests that it comprises 1st and 2nd modules involved in the nystatin polyketide backbone biosynthetic pathway, as the only two proximal methylmalonyl CoAs incorporated in nystatin molecule are the first two extender units. NysC protein of 11096 aa, the largest, to our knowledge, bacterial polypeptide discovered so far, is composed of 6 modules apparently responsible for the condensation steps 3 to 8 in nystatin polyketide chain biosynthesis (incorporation of C21 - C32). Module 5 of the NysC protein contains an ER domain, which is accountable for the reduction of the double bond between C29 and C28 (see Fig. 1). Besides module 5, all other modules in NysC are similar in that they all contain KS, AT, DH, KR and ACP domains. It was noticed that KR domains in modules 4 and 5 are 100% identical on the aa sequence level, and 99.9% identical at the level of DNA sequences encoding these domains. Thus, KR domains in modules 4 and 5 most probably represent an example of a relatively recent duplication in the process of evolution. NysI C-terminally truncated protein of 7066 aa, for which aa sequence information at the C-terminus is still missing, is composed of at least 4 complete modules. All these modules contain KS, AT, DH, KR and ACP domains, but the DH domains in three modules are apparently inactive, suggesting that the known part of NysI PKS is responsible for the elongation steps 9 through 12 (incorporation of C13 - C20). This assumption is further supported by the fact that the AT domain in

module 11 (based on sequence similarity) is specific for methylmalonylCoA extender, while all other AT domains in NysA, NysC and NysI are malonyl CoA-specific. Thus, the AT domain in module 11 is presumably responsible for the occurrence of the methyl group at C16 on the nystatin polyketide backbone, which is later oxidized to give a C16-coupled carboxyl (see Fig. 1).

Downstream of the *nysC* gene, a coding sequence *nysE* for thioesterase, presumably responsible for the release of mature polyketide chain from the nystatin PKSs, was found. The *nysR1*, *nysR2* and *nysR3* genes, were found downstream of *nysE*. The products of these genes are homologous to the presumed transcriptional regulators. NysR1 (966 aa), NysR2 (953 aa), and NysR3 (927 aa) proteins were all found to contain putative helix-turn-helix (HTH) DNA binding motifs of LuxR type at their C-termini. Beside that, NysR1 contained a distinct ATP/GTP binding motif, and NysR3 contained a "leucine zipper" (putative DNA binding) motif at their N-termini. The gene encoding NysR1 was found to contain a rare TTA codon (for Leu11) close to the beginning of the gene, suggesting that NysR1 expression might be regulated in *S. noursei* at the level of translation by a *bldA*-like gene (White & Bibb, J. Bacteriol, v. 179: 627-633, 1997).

In order to confirm the involvement of *nysR1* gene in the nystatin biosynthesis a gene disruption experiment was performed with the use of a 1379 bp *Apa*I DNA fragment internal for the *nysR1* coding sequence. The 1379 bp *Apa*I DNA fragment internal for the *nysR1* coding sequence and representing nt 51531-52910 of SEQ ID NO 1 was cloned into the *Apa*I site of the pGEM11Zf(-) vector, giving the recombinant plasmid pNRD1. The 1430 bp *Eco*RI/*Hin*dIII DNA fragment isolated from pNRD1 was ligated with the 3.0 kb *Eco*RI/*Hin*dIII fragment of pSOK201 resulting in the pNRD2 vector. The latter was subsequently used for *nysR1* gene disruption in *S.*

noursei ATCC11455 via conjugation from *E. coli* ET12567 (pUZ8002).

Analysis of the nystatin production by the *nysR1* disruption mutant revealed that it is not capable of producing nystatin. It shall be noted, however, that the phenotype observed for the *nysR1* disruption mutant, might reflect the polar effect of mutation on the *nysR2* and *nysR3* genes, which can be co-transcribed with *nysR1*.

Downstream of *nysR3*, the genes *nysR4*, *nysR5*, ORF1, and ORF2 were found. The *nysR4* gene product of 210 aa (this has subsequently found to be 266 aa expression from an upstream start codon at nucleotide 120628 in SEQ ID No. 35) shows similarity to transcriptional activators of response regulator type, and contains centrally located ATP/GTP binding and C-terminally located LuxR-type HTH DNA binding motifs. NysR5 protein of 253 aa displays similarity to the transcriptional repressors, and contains a putative DeoR-type HTH DNA binding motif at its N terminus. It seems likely that *nysR4* and *nysR5* gene products are involved in regulation of nystatin biosynthesis based on their location proximal to the nystatin biosynthesis genes. ORF2, located downstream of *nysR5*, and transcribed in the opposite direction, encodes a 354 aa peptide showing similarity to transcriptional activators and having centrally located putative HTH DNA binding motif of AsnC type. Whether this gene is involved in regulation of nystatin biosynthesis is not apparent, as ORF1, located immediately upstream of ORF2, encodes a putative peptidase. It seems likely that ORF2 is rather involved in regulation of ORF1, but to confirm this, experimentation on ORF2 inactivation is required. The fact that the gene encoding a peptidase, for which no role in nystatin biosynthesis could be assigned, was found on the right flank of the sequenced region, suggests that the right border of the nystatin biosynthesis gene cluster had been identified.

On the left flank of the sequenced region encompassing the genes described above, two genes located upstream of *nysA*, and transcribed in the direction opposite to *nysA* were identified (Fig. 4). The *nysD1* gene product of 506 aa displays considerable homology to the UDP-glucuronosyltransferases from mammals. This enzyme belongs to the UDP-glycosyltransferase family, and takes part in the process of elimination of potentially toxic xenobiotics by the way of their glycosylation. It seems likely that NysD1 represents a glycosyltransferase responsible for the attachment of the deoxysugar moiety (mycosamine) to the nystatin polyketide backbone. The product of *nysD2* shows a high degree of homology to the perosamine synthetases and transaminases responsible for the attachment of amino groups to the deoxysugars in the process of their biosynthesis. Thus, NysD2 presumably represents an aminotransferase involved in mycosamine biosynthesis.

Beside *nysI* encoding PKS type I, four other genes were identified within the second sequenced region (SEQ ID NO. 2) of the nystatin biosynthesis gene cluster of *S. noursei* ATCC11455 (Fig. 4). The 344 aa protein encoded by the *nysD3* gene is highly homologous to the GDP-mannose-4,6-dehydratases required for deoxysugar formation. It is thus likely that the NysD3 protein is involved in biosynthesis of the nystatin mycosamine moiety in *S. noursei* ATCC11455. *nysH* and *nysG* gene products of 584 aa and 605 aa, respectively, display a high degree of similarity to transporters of the ABC family. Both NysH and NysG polypeptides contain a distinct ABC transporter signature at their C-termini, centrally located ATP/GTP binding motifs, and N-terminally located transmembrane regions. These two proteins most probably are responsible for the ATP-dependent active efflux of nystatin from the producing organism, thus eliminating the danger of

membrane clogging by the hydrophobic nystatin molecules. The product of the *nysF* gene, a 245 aa polypeptide, displays homology to the 4'-phosphopantetheine transferases. The latter enzyme is responsible for the post-translational modification of the ACP domains of the PKSs, and is required for its full functionality (Cox et al., *FEBS Lett.*, v. 405: 267-272, 1997; Kealey et al., Proc. Natl. Acad. Sci. USA, v. 95: 505-509, 1998). It seems likely, therefore, that the NysF protein functions in post-translational modification of nystatin PKSs, and is required for nystatin biosynthesis.

Example 2 - Genetic manipulation of the nystatin PKS genes leading to production of novel polyene antibiotics

Nystatin belongs to the group of the polyene macrolide compounds, which are characterized by having 3 to 8 conjugated double bonds in their macrolactone ring. Nystatin itself is a tetraene, having 4 conjugated double bonds between C20 and C27. There is also a set of 2 conjugated double bonds on the nystatin molecule, between C30 and C33, which is separated from the set of 4 conjugated double bonds by C28-C29 (see Fig. 1). From the computer-assisted analysis of the NysC PKS it became apparent that the ER domain in module 5 in this protein is responsible for reduction of the double bond between C28 and C29. Thus, by inactivating this particular domain, it is theoretically possible to obtain a compound with a double bond between C28 and C29, thus joining two sets of conjugated double bonds in the nystatin molecule, and creating a heptaene macrolide compound.

To inactivate the ER domain in module 5 of NysC, the method of "in-frame" deletion within the *nysC* gene was chosen. The construction of the vector pERD4.2 for gene replacement in the NysC-encoding genomic region of

S. noursei was as follows:

Inactivation of ER domain in module 5 of NysC

PCR-assisted amplification of the 394 bp DNA fragment representing the coding sequence for the C-terminal part of the ER domain in module 5 of NysC, and the coding sequence for the N-terminal part of the KR domain in module 5 (nt 32174 - 32559), was performed. The oligonucleotide primer ERD1 (5'-GTTGGTACCCCACTCCCGGTCCGCAC-3', sense) (SEQ ID NO. 25) was selected from the nucleotide sequence of *nysC* gene comprising nt 32174-32190 (SEQ ID NO. 1) with additional nucleotides on the 5' end in order to create a *KpnI* restriction enzyme cleavage site. The oligonucleotide primer ERD2 (5'-CCAGCCGCATGCACCACC-3', antisense (SEQ ID NO. 26)) was selected from the *nysC* coding DNA sequence, and comprised the DNA segment between nt 32559-32542 (SEQ ID NO. 1) containing a *Sph*I restriction enzyme cleavage site. The resulting PCR fragment was digested with *Kpn*I and *Sph*I, and ligated together with the 1828 bp *Bam*HI/*Kpn*I DNA fragment (nt 29224-31052 of SEQ ID NO. 1), and the 1273 bp *Sph*I/*Eco*RI DNA fragment (nt 32548-33821 of SEQ ID NO. 1) into the *Eco*RI/*Bam*HI - digested pGEM3Zf(-) vector. The ligation mixture was transformed into the *E.coli* DH5α, and recombinant plasmid of 6.7 kb designated pERD4.1 was recovered from one of the transformants. The latter contained a hybrid DNA fragment representing nt 29224-33821 of the SEQ ID NO. 1 DNA sequence with internal deletion between nt 31052 and nt 32174 of the *nysC* coding region. This deletion eliminated the coding regions (aa 4837 to 5208 of *nysC*) for the part of the DH-ER interdomain linker and C-terminal part of the ER domain containing a putative NADP(H) binding site.

To construct the vector for inactivation of NysC ER4 domain in *S.noursei*, the recombinant DNA fragment was excised with *Eco*RI and *Hin*dIII restriction enzymes

from pERD4.1 and ligated with the 3.0 kb *Eco*RI/*Hin*dIII DNA fragment from pSOK201, and the ligation mixture was transformed into the *E.coli* DH5α. Plasmid pERD4.2 of 6.5 kb was isolated from one of the transformants and used to perform the gene replacement procedure in *S.noursei* ATCC11455 (see below). The recombinant *S.noursei* strains selected after this procedure were designated ERD44 and ERD48.

The latter plasmid was introduced into *S. noursei* ATCC11455 by intergeneric conjugation, and one transconjugant, *S. noursei* (pERD4.2), was chosen for further manipulations. After the correct mode of integration of pERD4.2 into the genome of the *S. noursei* (pERD4.2) was confirmed by Southern blot analysis, selection for the second crossover event was carried out as described in Sekurova et al., FEMS Microbiol Lett, v.177: 297-304, 1999 (and see below).

Gene replacement procedure

This method is carried out as described by Sekurova et al., 1999, supra.

The plasmid constructed for gene replacement as described above was introduced into *S.noursei* by conjugation from the *E.coli* ET 12567 (pUZ8002). One of the clones carrying the plasmid integrated into the chromosome via homologous recombination was subjected to three rounds of sporulation on antibiotic-free ISP2 agar medium, and the progeny after the third round was tested for the loss of antibiotic resistance marker. Southern blot analysis of the total DNA isolated from several antibiotic-sensitive strains with an appropriate probe was used to confirm the desired mutation.

Of 8 colonies, which had lost the selection marker, and thus undergone a second crossover event, 4 were shown by Southern blot analysis to have reverted to the wild-type genotype. Two strains were shown to contain a large deletion apparently eliminating a substantial

portion of the nystatin gene cluster, while two other mutants contained either the desired 1116 bp deletion (ERD44), or a deletion which was somewhat larger than expected (ERD48). Analysis of the polyene antibiotic production by the strains ERD44 and ERD48 revealed that they do not produce nystatin. Instead, ERD44 was shown to produce a polyene compound having UV spectrum peaks characteristic for heptaens (Figure 6), as expected. Surprisingly, the ERD48 mutant was shown to produce hexaenic polyenes (according to spectroscopic analysis), which would be consistent with "in-frame" deletion of the complete module 5 from the NysC protein. In order to investigate the event which occurred in the ERD48 mutant in more detail, the DNA fragment was PCR-amplified from the genome of *S. noursei* ERD48 mutant, which would encompass the putative product of such deletion (see below).

PCR-assisted amplification and cloning of the PKS-encoding DNA fragment from the S.noursei ERD48 genome

The PCR reaction aimed at amplification of part of the mutant *nysC* gene in *S.noursei* ERD48 was carried out with oligonucleotide primers KR48.1 (sense, 5'-CCG CGT CGG ATC CGC CGA C-3') (SEQ ID NO: 27) and KR48.2 (antisense, 5'-AGC CTT CGA ATT CGG CGC C-3') (SEQ ID NO: 28) which corresponded to the nt 24744-24760 and nt33818-33833, respectively, of the DNA sequence in SEQ ID NO. 1. The 50 μl PCR mixture contained 0.1 μg of *S.noursei* ERD48 total DNA, 25 pm of each KR48.1 and KR48.2 oligonucleotide primers, dNTPs (final concentration 350μm), 1xPCR buffer from Expand High Fidelity PCR System (Boehringer Mannheim) and 1.5 U of the DNA polymerase mixture from the same system. The PCR was performed on the Perkin Elmer GeneAmp PCR System 2400 with the following program: 1 cycle of denaturation at 96°C (4 min), 35 cycles of denaturation/annealing/ synthesis at 94°C (45 sec) and 70°C (10 min) and 1 full

cycle of final annealing/extension at 72°C (10 min). The 2.7 kb DNA fragment obtained with this procedure was digested with *Eco*RI and *Bam*HI restriction enzymes, and ligated with pGEM3Zf(-) vector DNA digested with the same enzymes. The ligation mixture was introduced into *E.coli* DH5α by transformation, the plasmid pKR48 of 5.9kb was isolated from one of the transformants and subjected to DNA sequence analysis.

The DNA sequence of the insert in pKR48 is present in SEQ ID NO. 29, (identified herein as ERD48 seq). The translation product is shown in SEQ ID NO. 30 and is a 899 aa protein - the molecule features of SEQ ID NOs 29 and 30 respectively are shown below:

SEQ ID NO: 29 (DNA; ERD48.seq)

Start	End	Name	Description
1	254	DH4	DH4 domain coding region, C-terminal
1170	1913	KR4/5	hybrid ketoreductase domain, module 4/5
2010	2231	ACP5	ACP5 domain coding region
2295	2700	KS5	KS5 domain coding region

SEQ ID NO: 30 (AA; translation product)

Start	End	Name	Description
1	84	DH4	DH4 domain module 4, C-terminus
390	637	KR4/5	hybrid KR domain
670	743	ACP5	ACP domain, module 5
764	899	KS5	KS domain, module 5, N-terminus

The cloning and DNA sequencing of this 2700 bp fragment confirmed that it encodes a part of a hybrid PKS module, which would be consistent with recombination

between DNA sequences encoding highly homologous KR domains in modules 4 and 5 of NysC. This recombination apparently has led to deletion of DNA sequences encoding C-terminal parts of KR and ACP domains of module 4, and KS, AT, DH, ER domains, and N-terminal part of the KR domain of module 5, thus resulting in the loss of one complete module from NysC PKS.

Preliminary analysis of the compounds produced by the *S. noursei* ERD44 and ERD48 was carried out. It was shown that a heptaenic compound produced by the ERD44 mutant has high antifungal activity against *Candida albicans*, an organism used in tests for antifungal activity. At this point it is not possible to accurately assay the activity of this compound (tentatively named S44), because it is not yet properly purified, and its exact concentration is difficult to estimate. However, some rough estimates based on the UV absorbance at the wave lengths characteristic for nystatin, S44, and amphotericin (a heptaenic macrolide), suggest that S44 might have 4-5 times higher antifungal activity compared to nystatin. HPLC analysis of the compounds produced by the ERD48 mutant suggests that at least 5 hexaenic macrolides with different retention times are produced by this strain (mixture called S48). This probably reflects the different states of modifications of the macrolactone ring by i.e. glycosylation at C19, hydroxylation at C10, or oxidation of the methyl group at C16. This could have been expected, since reduction of the macrolactone ring size most probably leads to the lower affinity of the modifying enzymes towards the new substrate.

Antifungal activity of the S48 mixture was tested, and found to constitute approx. 10% of nystatin activity. It seems probable that only one of the compounds in the S48 mixture produced by ERD48, which is fully decorated by the ring-modifying enzymes, is responsible for the antifungal activity detected. Thus,

relative antifungal activity of this compound is impossible to assess prior to its purification. Some of the hexane antibiotics are known to have antibacterial, as well as antifungal activity (Ciftci, et al., J. Antibiot, v. 37: 876-884, 1984). It is thus possible that hexaenic compounds produced by the ERD48 mutant can be used for production of antibacterial agents. The changes in the NysC protein leading to production of new polyene compounds in ERD44 and ERD48 mutants, along with the predicted structures of their macrolactone rings are presented in Fig. 5.

Inactivation of DH8 domain in module 8 of NysC

The possibility of genetically manipulating the nystatin PKS was further exemplified by inactivation of the DH domain in module 8 of NysC. The plasmid pNPR1.1 for gene replacement within *nysC* gene, which would result in in-frame deletion of the DNA region encoding DH8 domain was constructed as below:

The 3989 bp *Kpn*I/*Bcl*I DNA fragment (nt 43004-46993 of the region 1 DNA sequence (SEQ ID NO. 1) and the 2409 bp *Bam*HI/*Eco*RI DNA fragment (nt 47680-50089 of the same) were excised from the DNA of recombinant phage N1 and ligated with vector pGEM3Zf(-) DNA digested with *Eco*RI and *Kpn*I. The ligation mixture was transformed into *E.coli* DH5a, and recombinant plasmid pGEM-NPR1 was isolated from one of the transformants. The latter contained the hybrid DNA fragment representing the nt 43004-50089 of the region 1 DNA sequence (SEQ ID NO:1) with the internal deletion between nt 46993 and nt 47680. This deletion eliminated the DNA region encoding the aa 10150 to 10378 of the NysC polypeptide, thus affecting the DH8 domain in module 8, and DH8-KR interdomain linker in module 8. To construct the vector for inactivation of the NysC DH8 domain in *S.noursei*, the recombinant DNA fragment was excised with *Eco*RI and *Hind*III restriction enzymes from pGEM-NPR1 ligated with

the 3.0 kb *EcoRI*/Hind*III* DNA fragment from pSOK201 (see Fig. 3 and Table 3) and the ligation mixture was transformed into the *E.coli* DH5α. Plasmid pNPR1.1 of 9.4 kb was isolated from one of the transformants and used to perform the gene replacement procedure in *S.noursei* ATCC11455 according to Sekurova et al., 1999, supra.

The recombinant *S.noursei* strain selected after this procedure was designated NPR1.1 The *S. noursei* NPR1.1 recombinant strain was shown by Southern blot analysis to contain the desired deletion in the DH8-coding sequence of *nysC*. Analysis of the secondary metabolites in the culture extracts of the *S. noursei* NPR1 recombinant strain by thin layer chromatography (TLC) revealed the presence of presumed macrolide compounds. The relative mobility of these compounds differed from nystatin, and no UV spectra characteristic for nystatin could be detected in the extracts. It was suggested, that in the new molecule(s) produced by the NPR1 recombinant a set of 4 double bonds on the nystatin aglycone has been disturbed, and that the macrolactone ring now contains a hydroxy group attached at C23 (Table 5). No attempts to purify the compound(s) from NPR1 were made, as the bioassay against *Candida albicans* made with the NPR1 culture extracts showed very low antifungal activity. However, the NPR1 mutant can be potentially useful for further manipulations with the nystatin PKS.

Inactivation of KR domain in module 7 (NysC)

The 4404 bp DNA fragment was excised with *Eco*RI and *Sma*I restriction enzymes from the DNA of recombinant phage N1. The *Eco*RI site is situated in the polylinker of phage N1 to the left of the *S.noursei* DNA insert starting at nt 38398 of the region 1 DNA sequence (SEQ ID NO. 1), while *the Sma*I site corresponds to nt 42802 of the region 1 DNA sequence. The 3303 bp DNA fragment

was excised with *Sma*I and *Bam*HI restriction enzymes from the DNA of the same recombinant phage. The *Sma*I and *Bam*HI restriction sites are situated at nt 43099 and nt 46402 respectively, of the region 1 DNA sequence (SEQ ID NO. 1). Both DNA fragments were ligated with the pGEM3Zf(-) DNA digested with restriction enzymes *Eco*RI and *Bam*HI, and the ligation mixture was transformed in *Escherichia coli* DH5α. The plasmid pGEM-NPR2 of 10.7 kb was recovered from one of the transformants, which contained a recombinant DNA fragment which represented nt 38398-46402 of the region 1 DNA sequence (SEQ ID NO. 1) with the internal deletion between nt 42802 and nt 43099. This deletion results in elimination of the DNA region encoding aa 8753 to 8851 of the NysC protein encompassing a putative NADP(H) binding site in the KR domain of module 7. To construct the vector for inactivation of NysC KR7 domain in *S.noursei*, the recombinant DNA fragment was excised from pGEM-NPR2 with *Eco*RI and *Hin*dIII restriction enzymes, and ligated with the 3.0 kb *Eco*RI/*Hin*dIII DNA fragment from pSOK201, and the ligation mixture was transformed into the *E.coli* DH5α. Plasmid pNPR2 of 10.7 kb was isolated from one of the transformants and used to perform the gene replacement procedure in *S.noursei* ATCC11455 (according to Sekurova et al., 1999, supra). The recombinant *S.noursei* strain selected after this procedure was designated NPR2.1.

Analysis of the secondary metabolites in the culture extracts of the *S. noursei* NPR2.1 recombinant strain by TLC revealed the presence of presumed macrolide compounds. The relative mobility of these compounds differed from nystatin, and from the metabolites produced by NPR1 mutant. No UV spectra characteristic for nystatin could be detected in the extracts. It is suggested, that in the new molecule(s) produced by the NPR2.1 recombinant a set of 4 double bonds on the nystatin aglycone has been disturbed, and

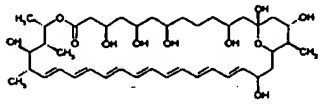
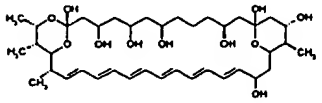
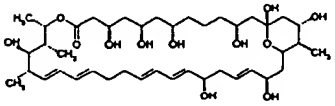
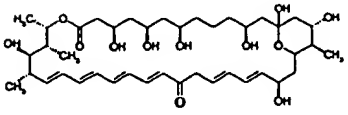
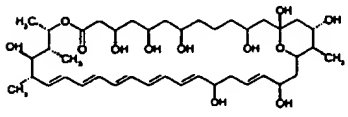
the macrolactone ring now contains a keto group at C25 (Table 5). No attempts at purification of the compound(s) from NPR2.1 were made, and no bioassays for antifungal activity with the NPR2.1 culture extracts were performed. This mutant has utility not only by virtue of the metabolites it produces, but also for further manipulation with nystatin PKS.

Inactivation of the ER domain in module 5 of the mutated NysC protein NysC_DH8)

To introduce the second mutation into the NysC protein with inactivated DH domain in module 8 (NysC_DH7), the plasmid pERD4.2 was introduced into the *S.noursei* mutant NPR1.1 and the gene replacement procedure was carried out as described in Sekurova et al., 1999, supra. This yielded recombinant *S.noursei* strain ERDH9 with mutations in both ER5 and DH8 coding sequences of *nys*C. The combination of these two mutations presumably leads to biosynthesis of the pentaenic nystatin derivative with a hydroxy group at C23 (Table 5). Preliminary analysis of the ERDH9 culture extracts confirmed that a polyene compound(s) is being produced by this strain although in quantities making identification of its true UV spectrum difficult. The preliminary data also show that this compound is preferentially accumulated in the culture supernatant, while nystatin produced by the wild-type *S. noursei* remains mostly associated with mycelium. This was consistent with the hypothesis that an additional hydroxy group on the nystatin molecule is responsible for increased water solubility of the compound(s). No attempts at purification of this new compound(s) were made, and no bioassays were performed.

To date, the Inventors have been unable to confirm the structure of the products of mutants NPR1.1, NPR2.1 and ERDH9.

Table 5. Predicted structures of nystatin derivatives produced via genetic engineering of *nysC* gene in *S. noursei* (see Example 2 for details)

Mutant	Expected structure (polyketide moiety only)	UV spectrum, nm (DMSO)	Activity
ATCC11455	nystatin (Fig. 1)	299, 312, 327	normal
ERD44		375, 395, 419, 444	high
ERD48		336, 352, 370, 391	low?
NPR1		-	low
NPR2.1		-	?
ERDH9		?	?

Example 3 - Manipulation of the regulatory genes leading to increased production of nystatin

Expression of nysR1 under the control of PermE* promoter in S. noursei ATCC11455

To further confirm that *nysR1* gene encodes a transcriptional activator of the nystatin biosynthesis genes, the latter was expressed in *S. noursei* ATCC11455 under the control of the PermE* promoter (Bibb et al., Mol. Microbiol., v. 14: 433-545, 1994). First, the plasmid pSOK804 for stable and efficient integration into the *S. noursei* ATCC11455 genome was constructed (Fig. 2). This was made by ligating together the 3.0 kb *Sph*I/*Hin*dIII DNA fragment from pSET152 (Bierman et al., 1992, supra) and 2.3 kb *Sph*I/*Hin*dIII fragment from bacteriophage VWB carrying functions necessary for site-specific integration (Van Mellaert et al., 1998, supra). Conjugation of pSOK804 from E. coli ET12567 (pUZ8002) into *S. noursei* ATCC1455 demonstrated that this plasmid integrates specifically into one site of the *S. noursei* genome at a frequency of $3\text{-}10^{-6}$.

To clone the *nysR1* gene under PermE* promoter in pSOK804, the following procedure was employed. The N-terminal part of *nysR1* was PCR-amplified from the recombinant phage N1 DNA template with the oligonucleotide primers NR1.1 (sense) 5'-CGCCGCATGCTGTTCTCACCCCACGT-3' (SEQ ID NO: 31), and NR1.2 (antisense): 5'-GGCGCGACCCGGTTCGGCCT-3' (SEQ ID NO: 32). The oligonucleotide primer NR1.1 sequence corresponded to the nt 51376-51391 of SEQ ID NO: 1 with addition of nucleotides CGCCGCATGC at the 5' end to create a site for *Sph*I endonuclease. The oligonucleotide primer NR1.2 corresponded to the sequence complementary to nt 51964-51982 of SEQ ID NO: 1, and encompassed a restriction site for *Age*I endonuclease. A 0.6 kb fragment was PCR-amplified using the phage N1 DNA as a template under conditions decribed in Example 1, and digested with *Sph*I

and *Age*I. The digested 0.6 kb fragment was ligated together with a 2.8 kb *Age*I/*Eco*RI DNA fragment from the phage N1 insert (*Eco*RI site originating from the phage's polylinker) into pGEM7Zf(-) vector digested with *Sph*I and *Eco*RI. The 2.8 kb fragment used in this ligation corresponded to nt 51971-54814 of SEQ ID NO: 1, and encompassed the C-terminal part of *nysR1* and N-terminal part of *nysR2* (encoding the first 162 aa of NysR2). The recombinant plasmid obtained as a result of this ligation was designated pNRE1. The 3.5 kb *Sph*I/*Hin*dIII DNA fragment from pNRE1 was ligated together with the 0.3 kb *Eco*RI/*Sph*I fragment from pGEM7ermELi (see Table 3) containing PermE* promoter into pSOK804 vector digested with *Eco*RI/*Hin*dIII. The resulting plasmid, pNRE2, was introduced into the *S. noursei* ATCC11455 by conjugation (see Example 1) yielding recombinant strain *S. noursei* (pNRE2). Analysis of the nystatin production by the latter strain in shake-flasks with reduced glucose medium revealed that it produces 50% more nystatin compared to the wild-type strain, most likely due to overexpression of the *nysR1* gene from the PermE* promoter. It therefore appears that *nysR1* gene encodes a positive activator that may be used for enhancing the production of nystatin and its derivatives in *S. noursei* strains.

Partial deletion of nysR5 gene in the S. noursei ATCC11455

To confirm the function of the *nysR5* gene predicted through analysis of its coding DNA sequence (see Example 1) in the regulation of nystatin biosynthesis, a specific mutation in *S. noursei* ATCC11455 genome was introduced. A DNA fragment from the *S. noursei* ACTT11455 genome encompassing nt 62037-63360 of the nucleotide sequence reported here was amplified by PCR with the primers NR5D1 (5'-GCGAGCGGCCGCTTCACCCCGCAACTCA-3') (SEQ ID NO: 33) and NR5D2 (5'-

CGCGAAGCTTGGCCGACTGCTCGACGTC-3') (SEQ ID NO: 34). The conditions for PCR were as described above. The 1341 bp PCR product was digested with *Not*I and *Hin*dIII, and ligated with the 1688 bp *Eco*RI/*Not*I DNA fragment (nt 60301-61989) and 3.0 kb *Eco*RI/*Hin*dIII fragment from pSOK201. The resulting plasmid, pNR5D, contained the *S. noursei* DNA fragment with a 43 bp deletion in the coding region of *nysR5* gene. This deletion creates a frame-shift mutation within the *nysR5* coding region, subsequently leading to truncation of its product. As a result of such truncation, 165 C-terminal amino acids of NysR5 are eliminated, and replaced with 14 amino acids encoded by another reading frame (and thus unrelated to NysR5). The pNR5D plasmid was used to perform a gene replacement procedure in *S. noursei* ATCC11455 as described in Sekurova et al., 1999, supra.

The mutation introduced through gene replacement led to a 5-15% increase in nystatin production by the resulting recombinant strain NR5D, compared to the wild-type *S. noursei*. Subtle but reproducible positive effect of NysR5 C-terminal deletion on nystatin biosynthesis correlates well with the putative repressor function assigned to this protein based on computer analysis (see Example 1). Since the deletion introduced in the *nysR5* gene does not eliminate the N-terminally located putative helix-turn-helix motif identified in this protein, the residual repressor activity of the truncated NysR5 polypeptide could account for the relatively small effect of this mutation on nystatin production. Nevertheless, this result confirms the usefulness of introducing mutations in the repressor-encoding gene as further means for enhancing the production of nystatin and its derivatives.

Example 4 - Completion of the sequencing of the nystatin biosynthesis gene cluster

The DNA sequence spanning the gap between SEQ ID No. 1 and SEQ ID No. 2 was determined for both DNA strands on the overlapping inserts in recombinant phages N20, N32, N95, N98, and N99 covering this region.

Procedures used for sequencing, probe generation and screening were as described in Example 1. The probes used for library screening, and the relevant recombinant phages discovered were as follows:

PKS 72	N20, N32
L44ES3.5	N90
L76SN0.5	N95
L20S0.64	N98, N99

Description of the probes:

6. L44ES3.5 probe. The 3.5 kb DNA fragment isolated from the phage N44 with restriction enzymes *Eco*RI and *Sal*I, was used as a L44ES3.5 probe.

7. L76SN0.5 probe. The 0.5 kb DNA fragment isolated from the recombinant phage N76 with restriction enzymes *Sac*I and *Not*I, was used as a L76SN0.5 probe.

8. L20S0.64 probe. The 0.64 kb DNA fragment isolated from the plasmid pL20EB3.7 with the restriction enzyme *Sal*I, was used as a L20S0.64 probe.

New sequence information resulted in identification of complete *nysI* and *nysDII* genes, as well as the new genes *nysJ*, *nysK*, *nysL*, *nysM*, and *nysN* (see Figure 7). According to the new information, the NysI protein of 9477 aa (SEQ ID No. 37) represents a PKS composed of six modules, responsible for the elongation steps 9 to 14 of the nystatin polyketide backbone biosynthesis. All these modules contain KS, AT, DH, KR and ACP domains. The presence of a mAT domain in module 11 is consistent with incorporation of methylmalonyl-CoA extender at this

elongation step. The DH domains in modules 10, 11, 12, and 14 seem to be inactive due the absence of the active site motif $H(X_3)G(X_4)P$. The KR domain in module 13 of NysI lacks the conserved motif aSRrG, and thus appears to be inactive. The latter feature, together with an inactive DH domain in module 11, most probably account for the presence of a six-membered ketalic ring (between C13 and C17) on the nystatin molecule.

The *nysJ* gene encoding a PKS, is located downstream of *nysI*, and is transcribed in the same direction. As judged from the organisation of modules in NysJ (SEQ ID No. 38), the latter is required for the elongation steps 15 to 17 in the nystatin macrolactone ring assembly. The DH domains in modules 16 and 17 within NysJ seem to be inactive, and the ER domain localized in module 15 is most probably responsible for the reduction of a double bond between C8 and C9.

The last, 18th module in the nystatin PKS system is represented by the NysK protein (SEQ ID No. 39) encoded by the *nysK* found downstream of *nysJ*. The NysK protein of 2066 aa is composed of KS, AT, inactive DM, ACP and TE domains. The NysK protein lacks a KR domain, and contains apparently inactive DH domain. A TE domain was identified at the C-terminus of NysK, suggesting that in addition to the condensation of the last extender unit, this protein also participates in the release of the mature nystatin polyketide chain from the PKS complex.

The gene organisation of the cluster is shown in Figure 9 and Figure 8 sets out the proposed involvement of the various proteins encoded in the nystatin biosynthetic pathway.

To confirm the involvement of *nysI*, and *nysJ* in nystatin biosynthesis, these genes were disrupted in *S. noursei* via homologous recombination using the conjugative suicide vectors pKNI1, and pKNJ1. The construction of the above vectors for disruption experiments was as follows. A 3.8 kb *Eco*RI/*Bam*HI-

fragment internal for the *nysI*, and corresponding to nucleotides 23711-27541 of SEQ ID No. 35, was excised from N64 DNA and ligated into the corresponding sites of plasmid pGEM3Zf(-), resulting in plasmid pL64EB3.8. The *S. noursei* fragment cloned into pL64EB3.8 was excised from this plasmid with restriction enzymes *Eco*RI and *Hin*dIII, and ligated with the 3.0 kb *Eco*RI/*Hin*dIII-fragment from the vector pSOK201, resulting in plasmid pKNI1.

A 3.7 kb *Eco*RI/*Bam*HI-fragment internal for *nysJ*, and corresponding to nucleotides 43287-46992 of SEQ ID No. 35 was excised from phage N20 DNA, and ligated into the corresponding sites of plasmid pGEM3Zf(-), resulting in plasmid pL20EB3.7. The *S. noursei* fragment cloned into pL20EB3.7 was excised from this plasmid with restriction enzymes *Eco*RI and *Hin*dIII, and ligated with the 3.0 kb *Eco*RI/*Hin*dIII-fragment from the vector pSOK201, resulting in plasmid pKNJ1. Both pKNI1 and pKNJ1 constructs were transformed into *E. coli* ET 12567 (pUZ8002), and further transferred into *S. noursei* ATCC 11455 by conjugation, as described in Zotchev *et al.*, (2000) Microbiology 146: 611-619. No nystatin production was detected in either of the pKNI1 and pKNJ1 disruption mutants, thus confirming the requirement of the identified PKS's for nystatin biosynthesis.

Three genes encoding proteins presumably involved in modification of the nystatin molecule were identified between *nysK* and *nysDII*. Both the *nysL* and *nysN* genes encode P450 monooxygenases of 394 aa and 398 aa, respectively (SEQ ID Nos. 40 and 42 respectively), that are probably responsible for hydroxylation of the nystatin polyketide moiety at C10, and oxidation of the methyl group at C16. Which protein is responsible for which reaction is not yet clear, and additional experiments are required for exact placement of NysL and NysN in the nystatin biosynthetic pathway. The *nysM* gene apparently encodes a ferredoxin of 64 aa (SEQ ID

No. 41), which presumably constitutes a part of one or both P450 monooxygenase systems, and serves as an electron donor [O'Keefe, D.P. & Harder, P.A. (1991). Occurrence and biological function of cytochrome P450 monooxygenases in the actinomycetes. *Mol. Microbiol.* 5, 2099-2105].

The DNA sequences extending the region depicted on Figure 7 (SEQ ID No. 35) approximately 10 kb to the left (recombinant phage N90), and approximately 5 kb to the right (recombinant phage N69) were determined. No genes with plausible functions in the nystatin biosynthesis were found, suggesting that the entire nystatin gene cluster had been identified.

Thus, based on the complete sequence information for the nystatin biosynthetic gene cluster, the following genes are identified and their roles described as follows (see also Figures 8 and 9):

Table 6. Genes identified within the nystatin biosynthetic gene cluster of *S. noursei* ATCC 11455

Designation	Product	Putative function
nysF putative	4'-phosphopantheteine transferase	post-translational PKS modification
nysG	ABC transporter	efflux of nystatin
nysH	ABC transporter	efflux of nystatin
nysD3	GDP-mannose-4,6-dehydratase	mycosamine biosynthesis
nysI	PKS type I	nystatin PKS (modules 9-14)
nysJ	PKS type I	nystatin PKS (modules 15-17)
nysK	PKS type I	nystatin PKS (module 18 + TE)
nysL	P450 monooxygenase	hydroxylation at

		C-10
nysM	ferredoxin	electron transfer in P450 system
nysN	P450 monooxygenase	oxidation of methyl group at C-16
nysD2	aminortansferase	mycosamine biosynthesis
nysD1	glycosyltransferase	attachment of mycosamine
nysA	PKS type I	nystatin PKS (loading module)
nysB	PKS type I	nystatin PKS (modules 1 and 2)
nysC	PKS type I	nystatin PKS (modules 3-8)
nysE	thioesterase	release of polyketide chain from PKS
nysR1	transcriptional activator	regulation of nystatin production
nysR2	transcriptional activator	regulation of nystatin production
nysR3	transcriptional activator	regulation of nystatin production
nysR4	transcriptional activator	regulation
nysR5	transcriptional repressor	regulation
ORF2	transcriptional activator	regulation
ORF1	peptidase	peptide metabolism

Example 5 - Manipulation of nystatin biosynthetic genes:

Predictive examples presented below provide guidelines for the rational genetic manipulations of the nystatin biosynthetic genes aimed at specific chemical changes in the nystatin molecule. These manipulations are based on the current understanding of structure-function relashionship of the polyene antibiotics the number of conjugated double bonds and the presence of two ionisable groups (exocyclic carboxyl and aminogroup belonging to the deoxysugar moiety mycosamine).

Changing the number and positions of conjugated double bonds.

The conjugated double bonds within the nystatin macrolactone ring are formed as a result of two reductive steps performed by a PKS modules with ketoreductase (KR), and dehydratase (DH) activities. Further reduction of the double bond can be brought about by introducing a enoylreductase (ER) activity in such PKS modules. This shall result in the formation of a completely saturated bond instead of a double bond at a specific step of nystatin biosynthesis. The following manipulations can be proposed (compounds that theoretically can be produced as a result of these manipulations are presented on Figure 10):

- insertion of ER domain into module 3 (1)
- insertion of ER domain into module 4 (2);
- simultaneous inactivation of the ER domain in module 5 and insertion of the ER domain into module 3 (3);
- simultaneous inactivation of the ER domain in module 5 and insertion of the ER domain into module 4 (4);
- simultaneous inactivation of the ER domain in module 5 and insertion of the ER domain into module

7 (5);

- simultaneous inactivation of the ER domain in module 5 and insertion of the ER domain into module 8 (6);
- simultaneous inactivation of the ER domain in module 5 and insertion of the ER domain into module 9 (7);
- simultaneous inactivation of the ER domain in module 5 and insertion of the ER domains into modules 8 and 9 (8);
- simultaneous inactivation of the ER domain in module 5 and insertion of the ER domains into modules 7 and 8 (9);

These manipulations can be performed using the techniques for gene replacement described for *S. noursei* (Sekurova et al., FEMS Microbiol Lett, 177: 297-304, 1999). The materials for manipulations can be provided by the nystatin gene cluster itself, or other PKS gene clusters. The latter could be preferential from the point of view of genetic stability of the recombinant strains.

Removal/repositioning of the COOH group

Exocyclic carboxyl function of the polyene antibiotics is believed to play a crucial role in selective toxicity of these compounds. More specifically, the inter- and intramolecular interactions between the ionizable exocyclic carboxyl and amino group of micosamine moiety seem to be of particular importance (Resat, H., Sungur, F.A., Baginski, M., Borowski, E., Aviyente, V. 2000. Conformational properties of amphotericin B amide derivatives - impact on selective toxicity. Journal of Computer-Aided Molecular Design, v. 14, p 689-703). It is theoretically possible to either remove the exocyclic carboxyl from, or reposition it on

the nystatin moleculevia manipulation of the nystatin biosynthetic genes. Nystatin derivatives produced via such manipulations could be useful on their own, or serve as substrates for further chemical modifications.

The following manipulations are proposed (resulting compounds are represented on Figure 11):

- replacement of methylmalonyl-specific acetyltransferase (AT) domain in module 11 of the nystatin PKS with malonyl-specific AT domain (**10**);
- replacement of malonyl-specific AT domain in module 12 with methylmalonyl-specific AT domain with simultaneous replacement of methylmalonyl-specific AT domain in module 11 with malonyl-specific AT domain (**11**);
- replacement of malonyl-specific AT domain in module 10 with methylmalonyl-specific AT domain with simultaneous replacement of methylmalonyl-specific AT domain in module 11 with malonyl-specific AT domain (**12**);
- inactivation of P450 monooxygenase-encoding genes *nysL* or *nysN* (whichever is found to be responsible for oxygenation of the methyl group at C-16 on the nystatin molecule) (**13**).

It shall be noted that specificity of the P450 monooxygenase responsible for the appearance of the exocyclic carboxyl function can be engineered so that it fulfills its function on the new substrates. Such methods as site-specific or random mutagenesis along with error-prone PCR and DNA shuffling might prove useful for this purpose.

1.3. Introduction of additional hydroxyl functions (increasing water solubility).

Polyene antibiotics are very poorly soluble in water mostly due to a highly hydrophobic set(s) of

conjugated double bonds. Increasing water solubility can be an advantage in certain cases, as it expands pharmacologicxal properties of the drug (Golenser, J., Frankenburg, S., Ehrenfreund, T. & Domb, A.J. 1999. Efficacious treatment of experimantal leishmaniasis with amphotericin B-arabinogalactan water-soluble derivatives. *Antimicrob Agents Chemother.*, v. 43: 2209-2214). To increase the water solubility of nystatin, we suggest to introduce additional hydroxyl functions (hydrophilic) to the nystatin molecule. The following modifications of the nystatin biosynthetic genes can lead to the desired effect (resulting compounds depicted on Figure 12):

- inactivation of dehydratase (DH) domain in module 3 of the nystatin PKS (**14**);
- inactivation of DH domain in module 4 (**15**);
- inactivation of DH domain in module 3 with simultaneous inactivation of ER domain in module 5 (**16**);
- inactivation of DH domain in module 4 with simultaneous inactivation of ER domain in module 5 (**17**) ;
- inactivation of DH domain in module 7 with simultaneous inactivation of ER domain in module 5 (**18**);
- inactivation of DH domain in module 8 with simultaneous inactivation of ER domain in module 5 (**19**);
- inactivation of DH domain in module 9 with simultaneous inactivation of ER domain in module 5 (**20**);

Extension, truncation or rebuilding of the macrolactone ring.

Novel derivatives of a polyene antibiotic nystatin can be obtained also through truncation of the nystatin PKS, leading to derivatives with a smaller macrolactone

ring (as exemplified in example 2 for the ERD48 mutant). This can be achieved through deletion of one or more modules from the nystatin PKS. Such truncations can lead to production of polyketides with 36- to 6-membered lactone rings that potentially can be useful for further modifications and synthesis of novel pharmaceuticals. Extension of the nystatin macrolactone ring can be achieved through insertion of additional modules into the nystatin PKS. Such manipulations can also lead to production of the lead compounds for pharmaceutical applications.

The nystatin molecule can be completely rebuilt by the way of shuffling the PKS modules between the nystatin, or other PKSs so that completely new derivatives are produced. In this respect, the method disclosed in the patent WO 00/77181 can prove useful for making the recombinant DNA constructs serving this purpose.

Finally, the nystatin biosynthetic genes can prove useful for manipulation of other macrolide antibiotic biosynthetic pathways. Both PKS and modification enzymes can prove useful for such purposes. It seems likely that nystatin biosynthetic genes will be most useful for manipulation of other polyene antibiotic biosynthetic clusters, such as the one for pimaricin (Aparicio, J.F., Fouces, R., Mendes, M.V., Olivera, N., Martin, J.F. 2000. A complex multienzyme system encoded by five polyketide synthase genes is involved in the biosynthesis of the 26-membered polyene macrolide pimaricin in *Streptomyces natalensis*. Chem Biol, v. 7: 895-905). High degree of similarity on the protein level between the nystatin and pimaricin biosynthetic enzymes will most probably ensure that their hybrids are functional. On the other hand, different specificities of the heterologous modification enzymes might provide new tools for further structural changes on the molecules produced by genetically engineered strains.

Example 6: Further manipulations of the regulatory genes leading to increased production of nystatin

Expression of *nysRII* under control of the P*ermE promoter in *S. noursei* ATCC 11455**

To confirm the function of the *nysRII* gene predicted through analysis of its coding sequence (see Example 1), it was expressed in *S. noursei* ATCC 11455 under control of the P*ermE** promoter. The 2168 bp *Sal*I-*Bcl*I fragment from the phage N58 (representing C-terminal part of *nysRII*) was cloned into the *Sal*I-*Bam*HI digested pGEM11Zf(-), resulting in construct pC1A1. The 811 bp N-terminal part of the *nysRII* gene was PCR-amplified from the phage N58 template with the oligonucleotide primers NSR2.1 (5'-GCCGGCATGCGACGAA CAG GACGAGAGGT-3') (SEQ ID NO. 44.) and NSR2.3 (5'-GCCGTGGTCGACGAA GGC-3') (SEQ ID NO. 45). The conditions for PCR were as described above. The PCR fragment was digested with *Sph*I and *Sal*I, and ligated, together with the 2168 bp *Sal*I-*Hin*dIII fragment from pC1A1 into *SphI-Hin*dIII digested pGEM3Zf(-) vector, giving the plasmid pC2A1. From the latter, the 3.0 kb *Sph*I-*Hin*dIII fragment was isolated and ligated, together with the 0.3 kb *Eco*RI-*Sph*I fragment containing the PermE* promoter either with *Eco*RI-*Hin*dIII digested pSOK804 vector (generating plasmid pC3A1), or with the 3.0 kb *Eco*RI-*Hin*dIII fragment from pSOK201 (generating plasmid pC3E1). Since the pSOK804-based vectors integrate site-specifically in the *S. noursei* chromosome, the pC3A1 plasmid could be regarded as a construct for *nysRII* expression in-*trans*. Plasmid pC3E1, on the other hand, is a suicide vector capable of integrating into the *S. noursei* genome only via homologous recombination through the cloned *nysRII* gene, thus providing expression of the latter in-*cis*. Introduction of plasmids pC3A1 and pC3E1 resulted in recombinant strains C3A1 and C3E1, respectively. In the former strain P*ermE** promoter is placed upstream of both *nysRII* and *nysRIII* genes (in-

cis), while in the latter strain P*ermE** promoter is placed upstream of *nysRII* gene (in-*trans*). Nystatin production by the C3A1 and C3E1 strains was increased by 18% and 22%, respectively, compared to the wild-type *S. noursei*. Moreover, during fermentation experiments it was noticed that nystatin production by the C3E1 strain reached its maximum 24 h earlier than the wild-type strain. These data support the assumption that the *nysRII* gene encodes a positive regulator that may be used for enhancing the production of nystatin and its derivatives in *S. noursei* strains.

Expression of *nysRIV* under control of the P*ermE promoter in *S. noursei* ATCC 11455:**

The start codon for *nysRIV* was reassigned, and is likely to be located 48 nt upstream of the originally proposed start nucleotide. Thus, *nysRIV* presumably encodes a 226 aa (long) rather than a 210 aa (short) protein as was previously suggested. The long and short versions of the *nysRIV* gene were PCR-amplified from the N58 recombinant phage DNA with oligonucleotide primers NR4P3 (5 - CTCAGCATGCCGAAAGGATGGCGG-3') (SEQ ID NO. 46) and NR4P5 (5'-AGGCAAGCTTCGGCGACACGGGCGT-3') (SEQ ID NO. 47), or NR4P4 (5'-CTCAGCATGCGTACGACCGGCGGG-3') (SEQ ID NO. 48) and NR4P5, respectively. The conditions for PCR were as described above. The corresponding PCR products of 0.78 kb and 0.73 kb were digested with *Sph*I and *Hin*dIII, and ligated, together with the 0.3 kb *Eco*RI-*Sph*I fragment containing the P*ermE** promoter, with the *Eco*RI-*Hin*dIII digested pSOK804 vector, resulting in plasmids pNR4EL and pNR4ES, respectively. Both plasmids were introduced into *S. noursei* ATCC 11455 generating mutant strains NR4EL and NR4ES, respectively. Nystatin production by the strain NR4ES (expressing a 210 aa protein from the P*ermE** promoter) did not differ significantly from that of the wild-type *S. noursei* harboring only pSOK804, while the NR4EL recombinant

cis), while in the latter strain P*ermE** promoter is placed upstream of *nysRII* gene (in-*trans*). Nystatin production by the C3A1 and C3E1 strains was increased by 18% and 22%, respectively, compared to the wild-type *S. noursei*. Moreover, during fermentation experiments it was noticed that nystatin production by the C3E1 strain reached its maximum 24 h earlier than the wild-type strain. These data support the assumption that the *nysRII* gene encodes a positive regulator that may be used for enhancing the production of nystatin and its derivatives in *S. noursei* strains.

Expression of *nysRIV* under control of the P*ermE promoter in *S. noursei* ATCC 11455:**

The start codon for *nysRIV* was reassigned, and is likely to be located 48 nt upstream of the originally proposed start nucleotide. Thus, *nysRIV* presumably encodes a 226 aa (long) rather than a 210 aa (short) protein as was previously suggested. The long and short versions of the *nysRIV* gene were PCR-amplified from the N58 recombinant phage DNA with oligonucleotide primers NR4P3 (5 - CTCAGCATGCCGAAAGGATGGCGG-3') (SEQ ID NO. 46) and NR4P5 (5'-AGGCAAGCTTCGGCGACACGGGCGT-3') (SEQ ID NO. 47), or NR4P4 (5'-CTCAGCATGCGTACGACCGGCGGG-3') (SEQ ID NO. 48) and NR4P5, respectively. The conditions for PCR were as described above. The corresponding PCR products of 0.78 kb and 0.73 kb were digested with *Sph*I and *Hin*dIII, and ligated, together with the 0.3 kb *Eco*RI-*Sph*I fragment containing the P*ermE** promoter, with the *Eco*RI-*Hin*dIII digested pSOK804 vector, resulting in plasmids pNR4EL and pNR4ES, respectively. Both plasmids were introduced into *S. noursei* ATCC 11455 generating mutant strains NR4EL and NR4ES, respectively. Nystatin production by the strain NR4ES (expressing a 210 aa protein from the P*ermE** promoter) did not differ significantly from that of the wild-type *S. noursei* harboring only pSOK804, while the NR4EL recombinant

(expressing a 226 aa protein from the P*ermE** promoter) produced nystatin at a level 36 % above the wild-type level. These data suggest that the longer, 226 aa - long version, represents the actual NysRIV polypeptide. Moreover, these data support the assumption that *nysRIV* gene encodes a positive regulator that may be used for enhancing the production of nystatin and its derivatives in *S. noursei* strains.

Claims

1. A nucleic acid molecule comprising:

(a) a nucleotide sequence as shown in SEQ ID No. 35; or

(b) a nucleotide sequence which is the complement of SEQ ID No. 35; or

(c) a nucleotide sequence which is degenerate with SEQ ID No. 35; or

(d) a nucleotide sequence hybridising under conditions of high stringency to SEQ ID No. 35, to the complement of SEQ ID No. 35, or to a hybridisation probe derived from SEQ ID No. 35 or the complement thereof; or

(e) a nucleotide sequence having at least 80% sequence identity with SEQ ID No. 35; or

(f) a nucleotide sequence having at least 65% sequence identity with SEQ ID No. 35 wherein said sequence preferably encodes or is complementary to a sequence encoding a nystatin PKS enzyme or a part thereof.

2. A nucleic acid molecule as claimed in claim 1, said molecule comprising:

(a) a nucleotide sequence as shown in SEQ ID No. 1 and/or in SEQ ID No. 2; or

(b) a nucleotide sequence which is the complement of SEQ ID No. 1 and/or SEQ ID No. 2; or

(c) a nucleotide sequence which is degenerate with SEQ ID No. 1 and/or SEQ ID No. 2; or

(d) a nucleotide sequence hybridising under conditions of high stringency to SEQ ID No. 1 and/or SEQ ID No. 2, to the complement of SEQ ID No. 1 and/or SEQ ID No. 2, or to a hybridisation probe derived from SEQ ID Nos. 1 and/or 2 or the complements thereof; or

(e) a nucleotide sequence having at least 65% sequence identity with SEQ ID No. 1 and/or SEQ ID No. 2, wherein said sequence preferably encodes or is complementary to a sequence encoding a nystatin PKS enzyme or a part

thereof.

3. A nucleic acid molecule as claimed in claim 1 or claim 2 which comprises a nucleotide sequence having at least 70% sequence identity with SEQ ID No. 35, or SEQ ID No. 1 and/or SEQ ID No. 2, wherein said sequence preferably encodes or is complementary to a sequence encoding a nystatin PKS enzyme or a part thereof.

4. A nucleic acid molecule comprising a part of a nucleotide sequence as defined in claim 1 or claim 2, wherein said part is at least 15 nucleotides in length.

5. A nucleic acid molecule as defined claimed in claim 1, which does not comprise the nucleotide sequence encoding ORF 1 as set out in Table 1.

6. A nucleic acid molecule as defined claimed in claim 1, which does not comprise the nucleotide sequence encoding ORF 2 as set out in Table 1.

7. A nucleic acid molecule as claimed in any one of claims 1 to 6 which encodes one or more polypeptides, or comprises one or more genetic elements, having functional activity in the synthesis of a macrolide antibiotic or a polyketide moiety.

8. A nucleic acid molecule as claimed in claim 7, wherein said macrolide antibiotic or polyketide moiety is nystatin or a nystatin derivative.

9. A nucleic acid molecule as claimed in any one of claims 1 to 6, said molecule comprising one or more genes, and/or one or more regulatory sequences, and/or one or more modules, or enzymatic domains, or non-coding or coding functional genetic elements of a PKS gene cluster.

10. A nucleic acid molecule as claimed in any one of claims 3 to 9, comprising a nucleotide sequence defined by any one or more of the nucleotide "start" and "end" positions within SEQ ID Nos. 35, 1 or 2, as set out in Table 1.

11. A nucleic acid molecule as claimed in any one of claims 3 to 9, comprising a nucleotide sequence defined as lying between any one or more of the nucleotide sequences having the "start" and "end" positions within SEQ ID Nos. 35, 1 or 2, as set out in Table 1.

12. A nucleic acid molecule comprising a nucleotide sequence encoding one or more amino acid sequences selected from SEQ ID Nos 3 to 20 or 36 to 43, or a nucleotide sequence which is complementary thereto or degenerate therewith or comprising a nucleotide sequence which encodes one or more amino acid sequences which exhibit at least 60% sequence identity with any one of SEQ ID Nos. 3 to 20 or 36 to 43.

13. A nucleic acid molecule as claimed in claim 12 which encodes one or more amino acid sequences which exhibit at least 85% sequence identity with any one of SEQ ID Nos. 3 to 20 or 36 to 43.

14. A polypeptide encoded by a nucleic acid molecule as defined in any one of claims 1 to 13.

15. A polypeptide as claimed in claim 14, comprising:
(a) all or part of an amino acid sequence as shown in any one or more of SEQ ID Nos. 3 to 20 or 36 to 43; or
(b) all or part of an amino acid sequence which has at least 60% sequence identity with any one or more of SEQ ID Nos. 3 to 20 or 36 to 43.

16. A polypeptide as claimed in claim 14, wherein said amino acid sequence at (b) has at least 85% sequence identity with any one or more of SEQ ID Nos. 3 to 20 or 36 to 43.

17. A polypeptide as claimed in any one of claims 14 to 16 or claim 11 having functional activity in the synthesis of a macrolide antibiotic or polyketide moiety.

18. A polypeptide as claimed in any one of claims 14 to 17, comprising a functional region of any one of SEQ Nos. 3 to 20 or 36 to 43, said functional region being as defined in Table 2.

19. An expression vector comprising a nucleic acid molecule as defined in any one of claims 1 to 13.

20. A host cell or transgenic organism comprising a nucleic acid molecule as defined in any one of claims 1 to 13 or an expression vector as defined in claim 19.

21. A method for producing a polyketide or macrolide molecule, said method comprising expressing within a host cell a nucleic acid molecule as defined in any one of claims 1 to 13.

22. Use of a nucleic acid molecule as defined in any one of claims 1 to 13 in the preparation of a modified PKS system, or in the preparation of a modified polyketide molecule.

23. A method for preparing a modified PKS system, or a modified polyketide molecule, said method comprising modifying a nucleic acid molecule as defined in any one of claims 1 to 13 or introducing a nucleic acid molecule as defined in any one of claims 1 to 13 into a

further PKS-encoding nucleic acid molecule.

24. A method as claimed in claim 23, being a method of preparing a nucleic acid molecule which comprises a nucleotide sequence encoding a modified polyketide synthase enzyme or enzyme system, said method comprising (a) using a nucleic acid molecule as defined in any one of claims 1 to 13 as a scaffold and modifying one or more portions of the nucleic acid molecule that encode enzymatic or other functional activities; or

(b) introducing one or more portions of the nucleotide sequence that encode enzymatic or other functional activities into an alternative (i.e. different "second") PKS scaffold.

25. A method as claimed in claim 23, being a method of preparing a nucleic acid molecule comprising a nucleotide sequence encoding a modified nystatin PKS, wherein said modified nystatin PKS is derived from a nystatin PKS encoded by a nucleic acid molecule as defined in any one of claims 1 to 13, said nucleic acid molecule containing first regions which encode enzymatic or other functional activities and second regions which encode scaffolding amino acid sequences, said method comprising:

(a) modifying at least one said first region; or

(b) incorporating at least one said first region into a scaffolding-encoding second region from a different PKS-encoding nucleotide sequence.

26. A method of preparing a modified nystatin PKS as defined in claim 25, said method comprising expressing a nucleic acid molecule prepared as defined in claim 25 within a host cell under conditions whereby the modified nystatin PKS is expressed.

27. A modified PKS system derived from a nucleic acid molecule as defined in any one of claims 1 to 13 by a method as defined in any one of claims 23 to 26.

28. A modified PKS system as claimed in claim 27, comprising a modified nystatin PKS wherein one or more of the polypeptides of SEQ ID Nos. 3 to 20 or 36 to 43, or one or more of the enzymatic domains in one or more modules of SEQ ID Nos. 5 to 7, 20, or 37 to 39 are modified.

29. A modified PKS system as claimed in claim 27, comprising a modified nystatin PKS wherein

(i) the ER domain in module 5 of Nys C (amino acids 4953-5239 of SEQ ID No. 7) is inactivated; or

(ii) a module of Nys C (SEQ ID No. 7) is deleted; or

(iii) the DH domain in module 8 of Nys C (amino acids 10086-10289 of SEQ ID No. 7) is inactivated; or

(iv) the KR domain in module 7 of Nys C (amino acids 8812-9086 of SEQ ID No. 7) is inactivated.

30. A multiplicity of cell colonies comprising a library of colonies wherein each colony of the library contains a different modified PKS as defined in any one of claims 27 to 29.

31. A method of producing a library of PKS complexes or a library of polyketide molecules, said method comprising culturing a library of colonies as defined in claim 30.

32. A library of PKS complexes or a library of polyketide molecules obtained or obtainable by a method as defined in claim 31.

33. A combinatorial library of polyketides wherein the polyketide members of the library are synthesized by a modified PKS system as defined in any one of claims 27 to 29.

34. A host cell or transgenic organism containing (a) a nucleic acid molecule prepared by a method as defined in any one of claims 23 to 25 or (b) a modified PKS system as defined in any one of claims 27 to 29.

35. A polyketide produced or producible by a host cell or transgenic organism as defined in claim 34.

36. An antibiotic derived from a polyketide as defined in claim 35.

Nystatin A1

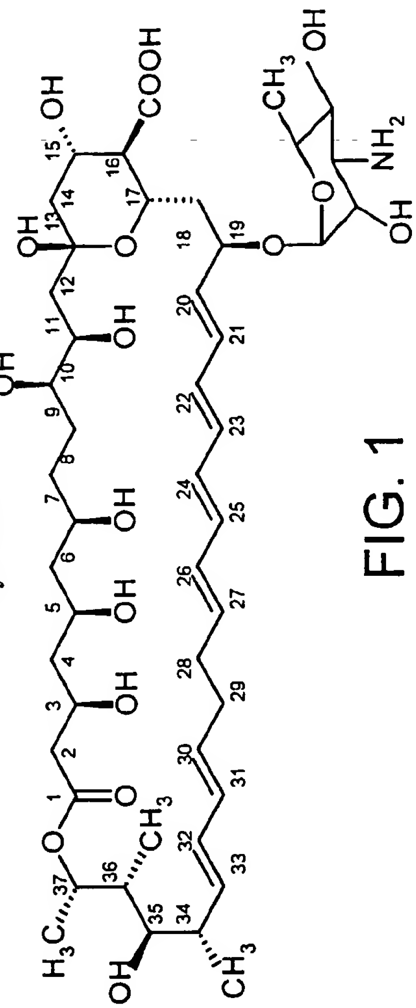
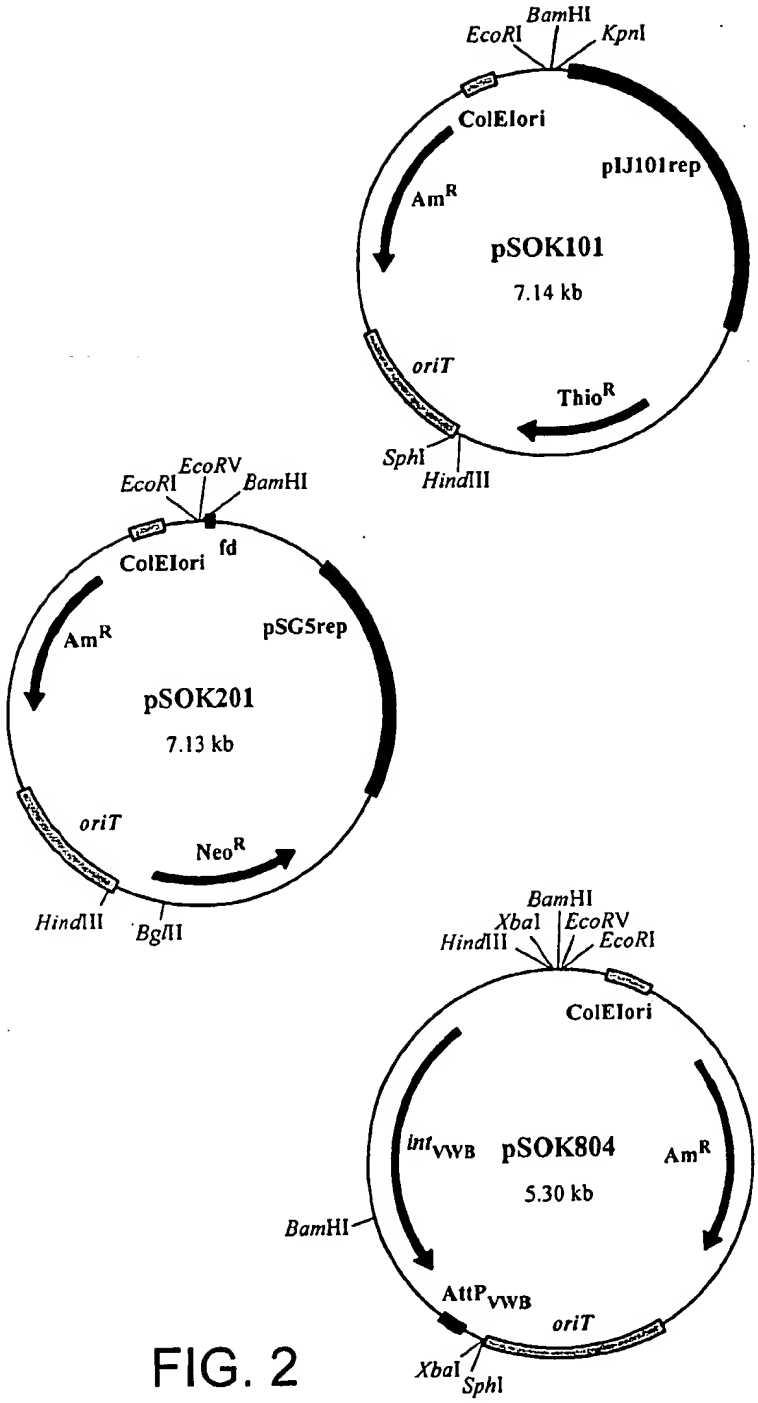


FIG. 1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KpnI
ColEIori
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Am^R
pSOK101
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Thio^R
SphI
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EcoRI
BamHI
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Am^R
pSG5rep
pSOK201
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oriT
Neo^R
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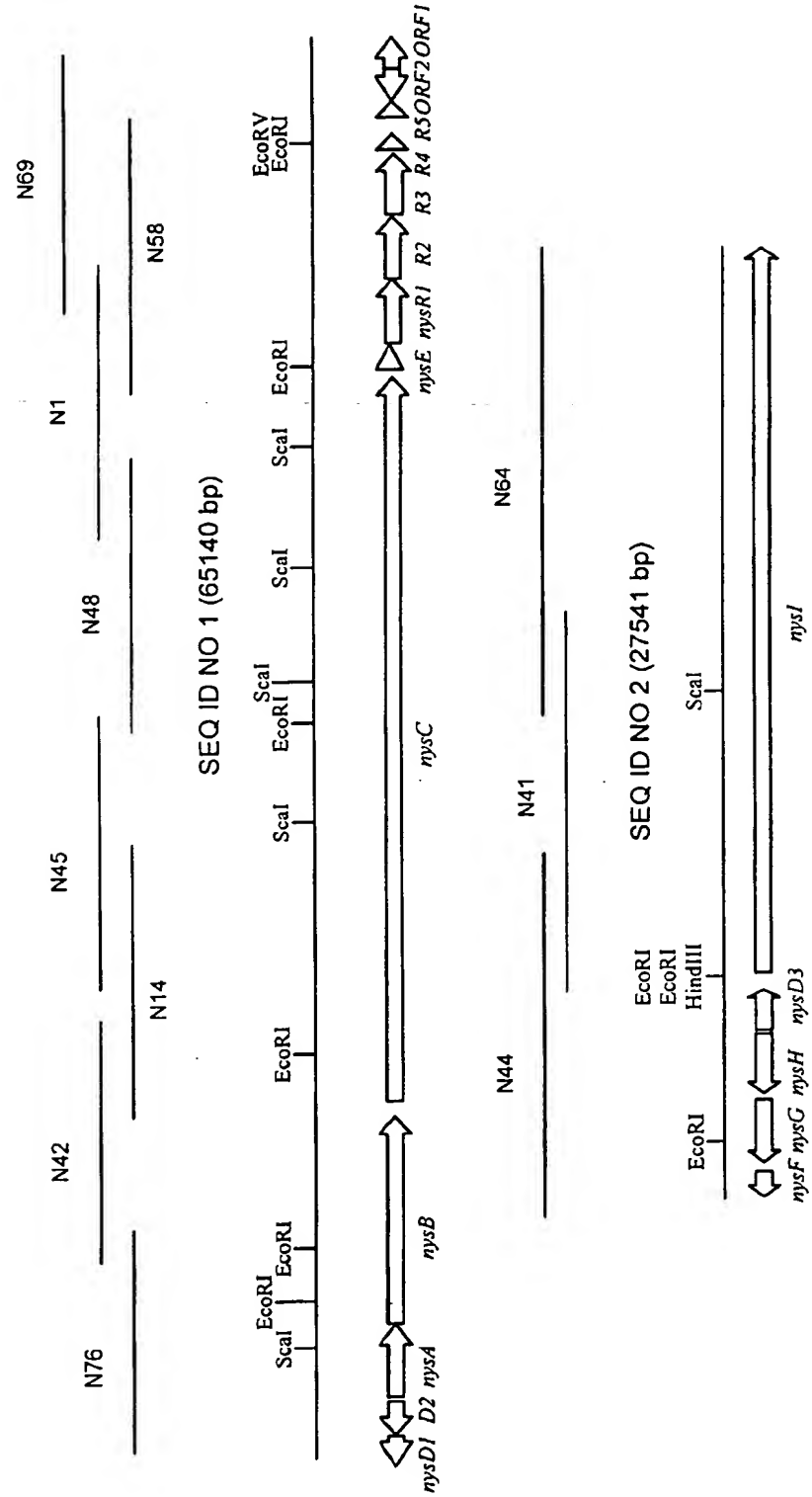
XbaI
SphI

FIG. 2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N1
N58
N48
N45
N14
N42
N76
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EcoRI
ScaI
EcoRI
ScaI
ScaI
EcoRI
ScaI
EcoRI
EcoRI
ScaI
nysE nysR1 R2 R3 R4 R5ORF2ORF1
nysC
nysB
nysA D2 nysD1
N64
N41
N44
SEQ ID NO 2 (27541 bp)
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EcoRI
EcoRI
HindIII
EcoRI
nysI
nysD3 nysH nysG nysF

FIG. 3

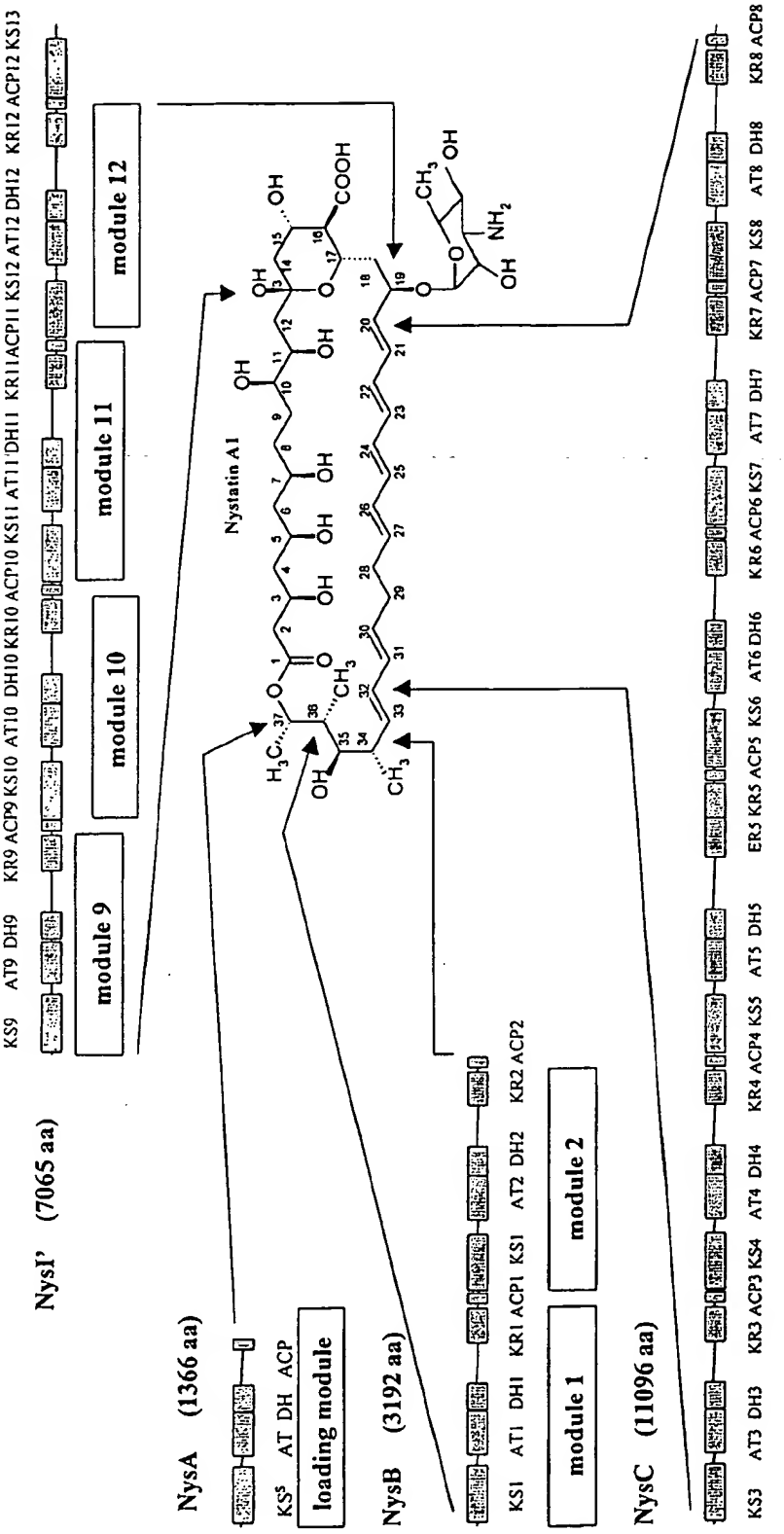

NysI' (7065 aa)
KS9 AT9 DH9 KR9 ACP9 KS10 AT10 DH10 KR10 ACP10 KS11 AT11 DH11 KR11ACP11 KS12 AT12 DH12 KR12 ACP12 KS13
module 9
module 10
module 11
module 12
Nystatin A1
NysA (1366 aa)
KS^5 AT DH ACP
loading module
NysB (3192 aa)
KS1 AT1 DH1 KR1 ACP1 KS1 AT2 DH2 KR2 ACP2
module 1
module 2
NysC (11096 aa)
KS3 AT3 DH3 KR3 ACP3 KS4 AT4 DH4 KR4 ACP4 KS5 AT5 DH5 ER5 KR5 ACP5 KS6 AT6 DH6 KR6 ACP6 KS7 AT7 DH7 KR7 ACP7 KS8 AT8 DH8 KR8 ACP8
module 3
module 4
module 5
module 6
module 7
module 8

FIG. 4

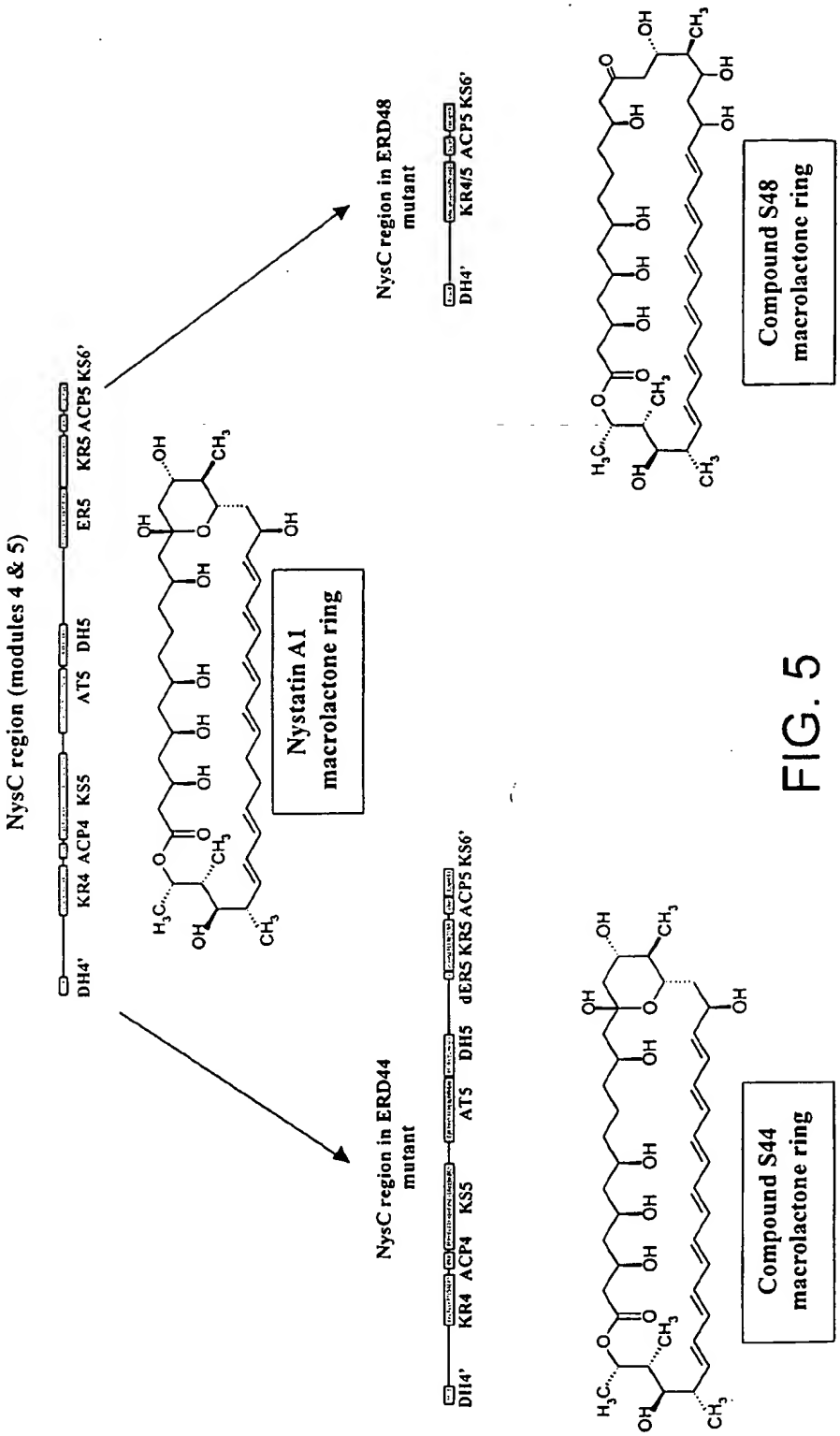

NysC region (modules 4 & 5)
DH4' KR4 ACP4 KS5 AT5 DH5 ER5 KR5 ACP5 KS6'
Nystatin A1 macrolactone ring
NysC region in ERD48 mutant
DH4' KR4/5 ACP5 KS6'
Compound S48 macrolactone ring
NysC region in ERD44 mutant
DH4' KR4 ACP4 KS5 AT5 DH5 dER5 KR5 ACP5 KS6'
Compound S44 macrolactone ring

FIG. 5

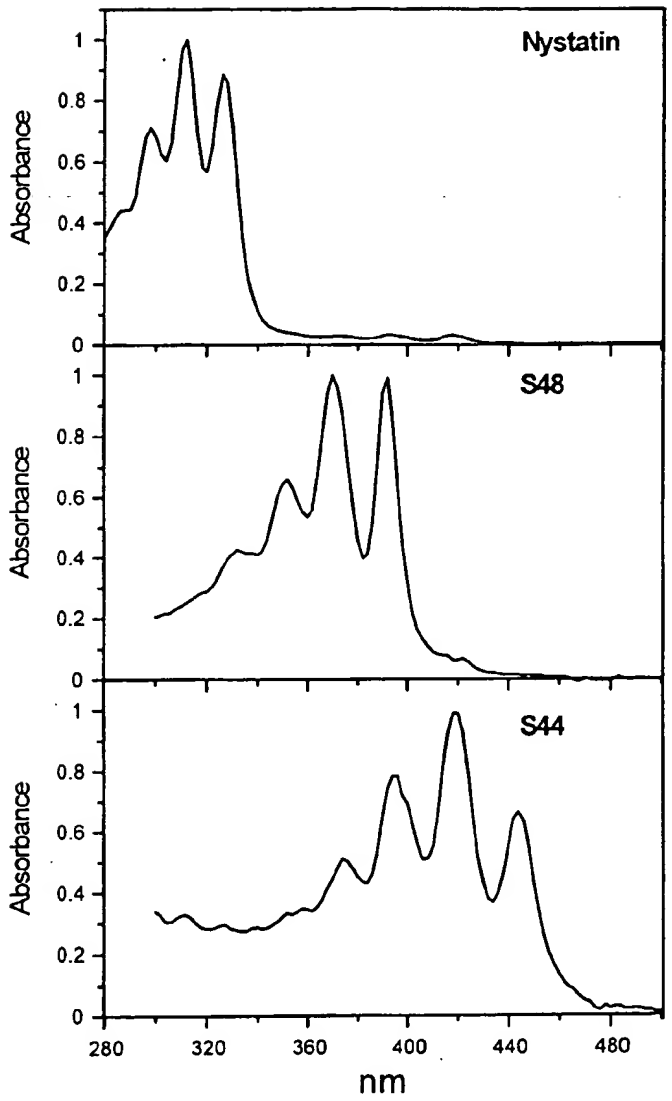

Nystatin
S48
S44
Absorbance
Absorbance
Absorbance
0
0.2
0.4
0.6
0.8
1
280
320
360
400
440
480
nm

FIG. 6

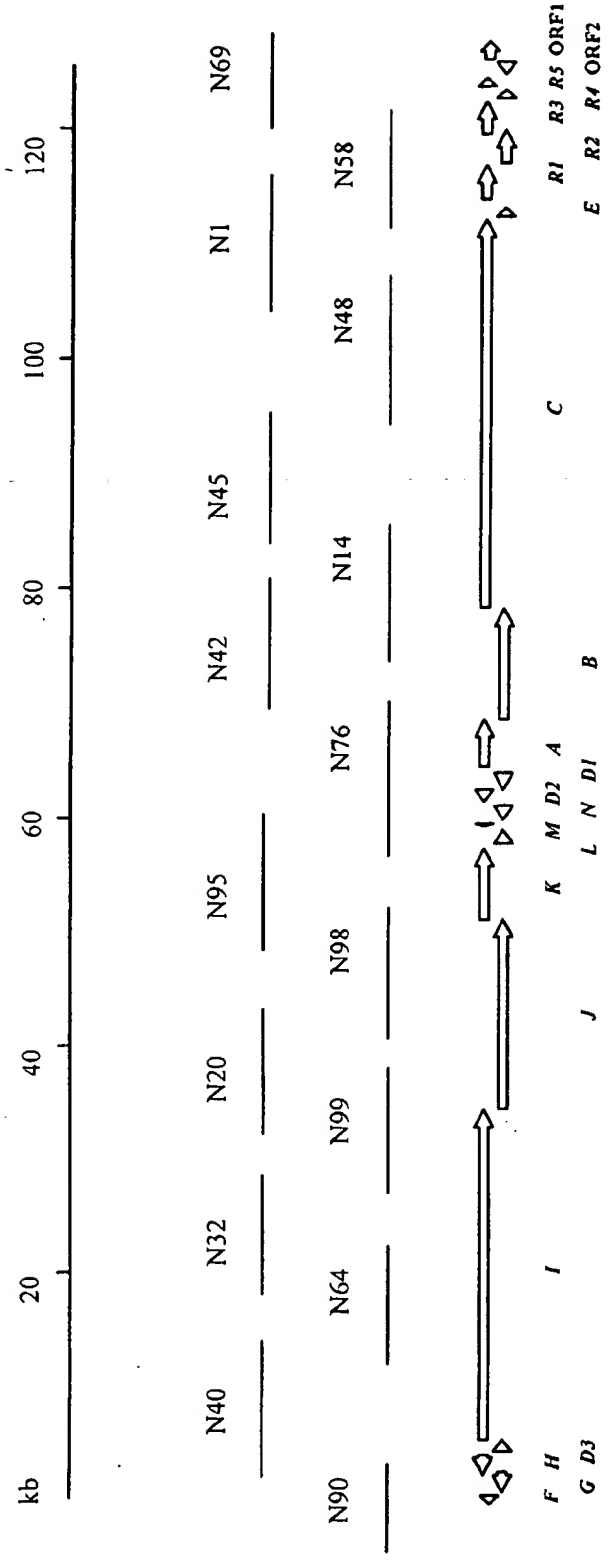

kb
20
40
60
80
100
120
N40
N32
N20
N95
N42
N45
N1
N69
N90
N64
N99
N98
N76
N14
N48
N58
F H
G D3
I
J
K M D2 A
L N D1
B
C
R1 R3 R5 ORF1
E R2 R4 ORF2

FIG. 7

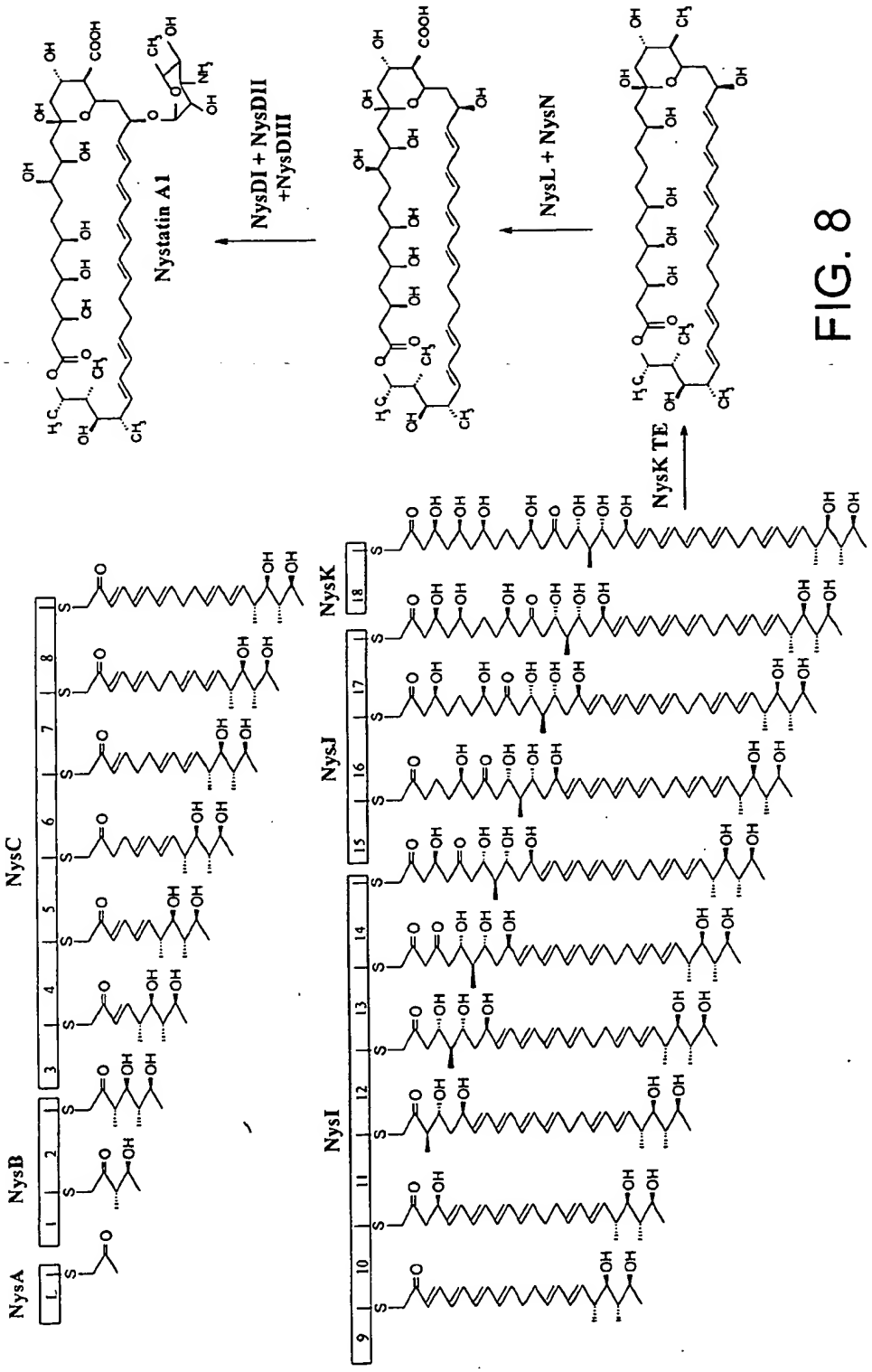

Nystatin A1
NysDI + NysDII
+NysDIII
NysL + NysN
NysK TE
NysA
NysB
NysC
NysI
NysJ
NysK

FIG. 8

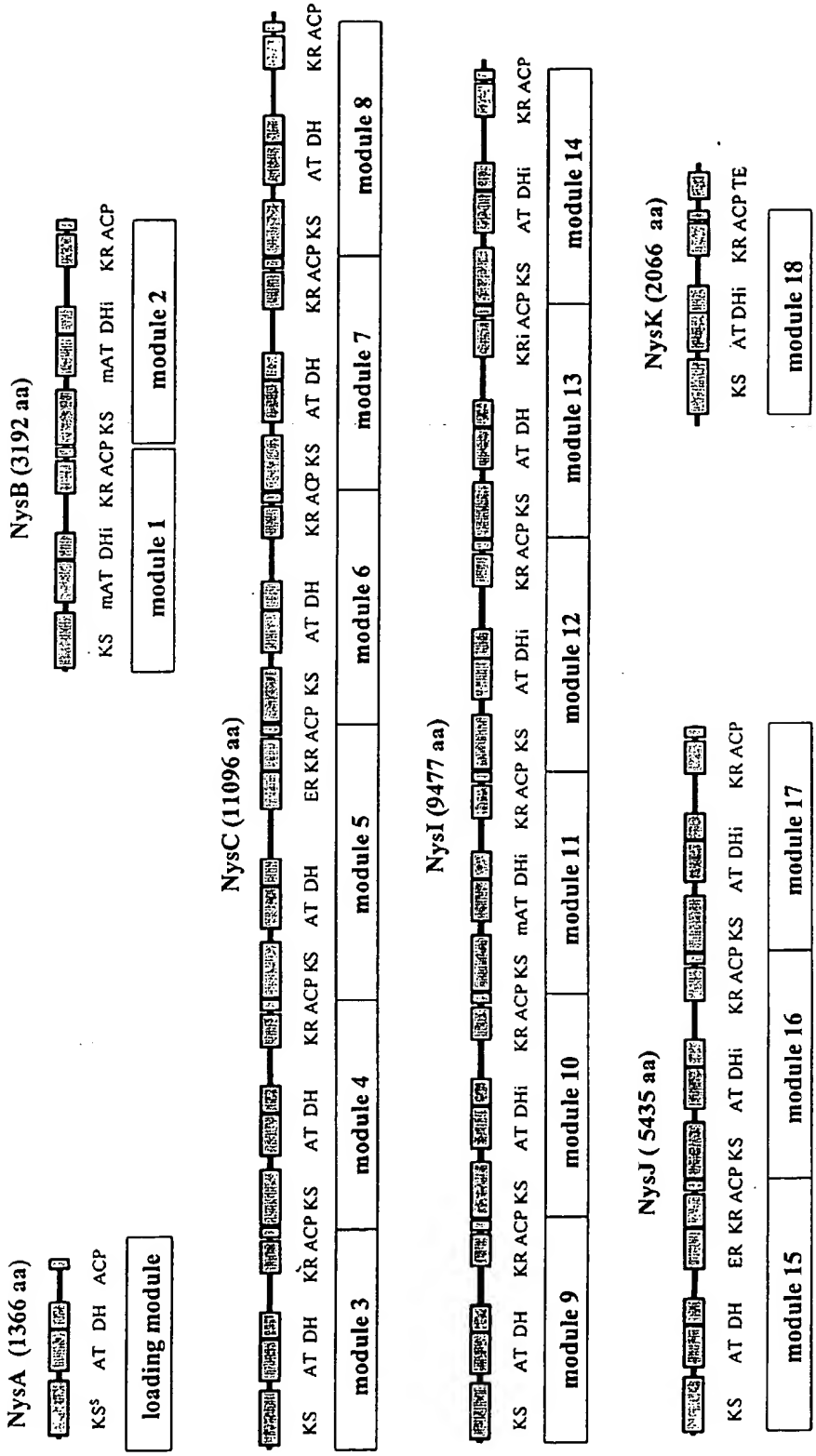

NysA (1366 aa)
KS^{s} AT DH ACP
loading module
NysB (3192 aa)
KS mAT DHi KR ACP KS mAT DHi KR ACP
module 1
module 2
NysC (11096 aa)
KS AT DH KR ACP KS AT DH KR ACP KS AT DH ER KR ACP KS AT DH KR ACP KS AT DH KR ACP
module 3
module 4
module 5
module 6
module 7
module 8
NysI (9477 aa)
KS AT DH KR ACP KS AT DHi KR ACP KS mAT DHi KR ACP KS AT DH KRi ACP KS AT DHi KR ACP
module 9
module 10
module 11
module 12
module 13
module 14
NysJ (5435 aa)
KS AT DH ER KR ACP KS AT DHi KR ACP KS AT DHi KR ACP
module 15
module 16
module 17
NysK (2066 aa)
KS AT DHi KR ACP TE
module 18

FIG. 9

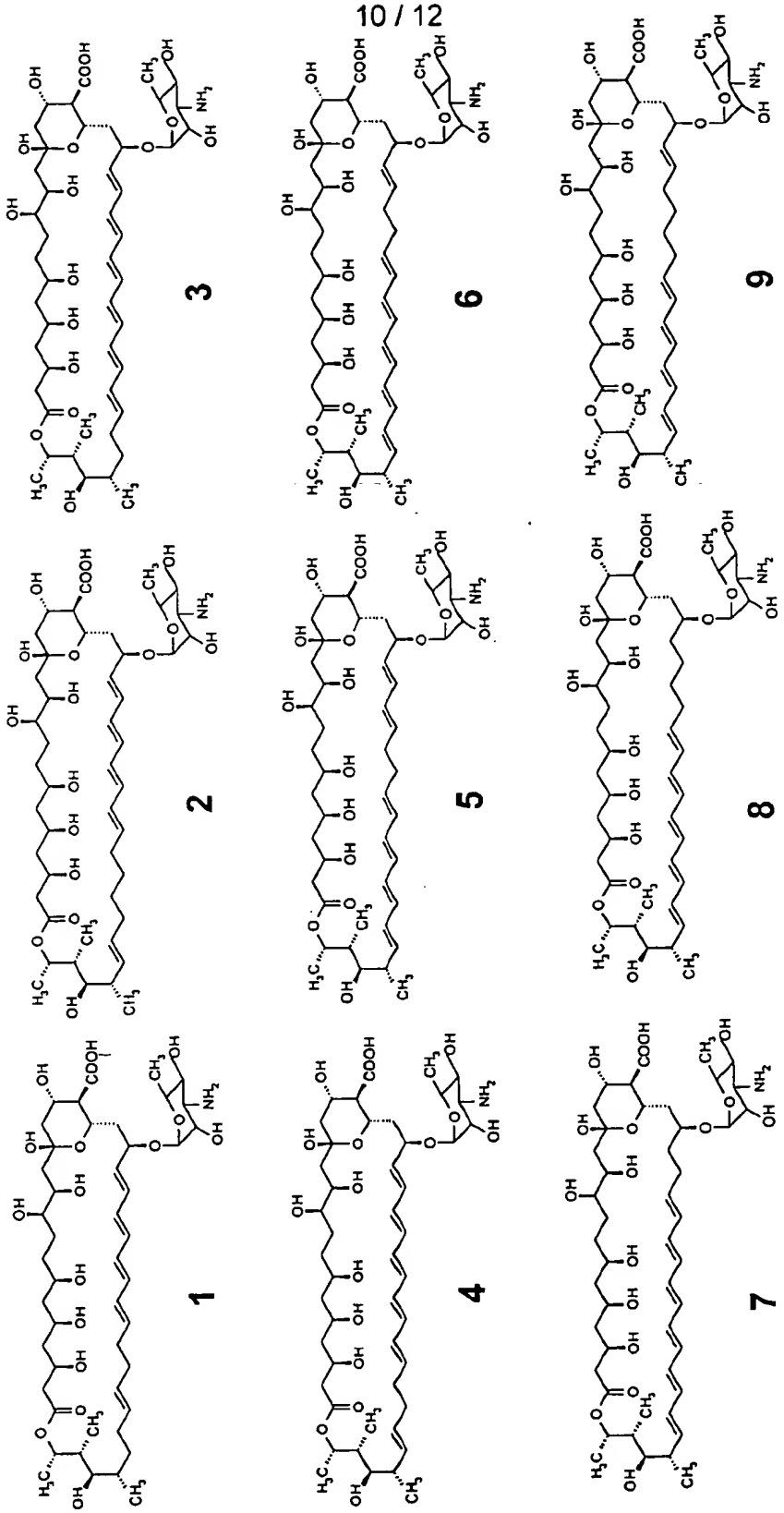
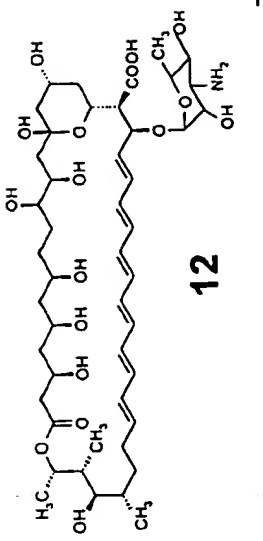
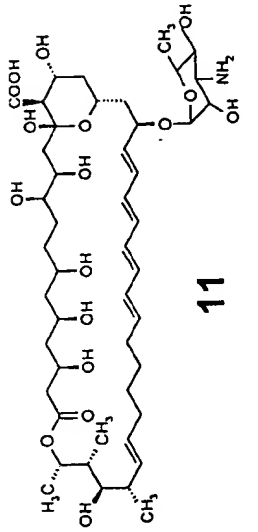


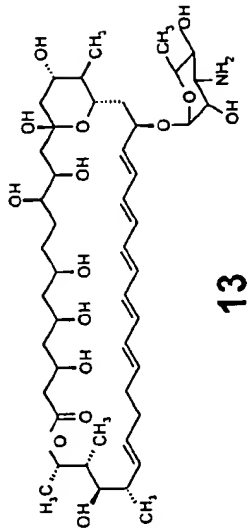
FIG. 10



12



11



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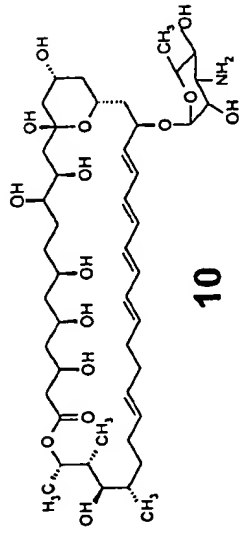

10

FIG. 11

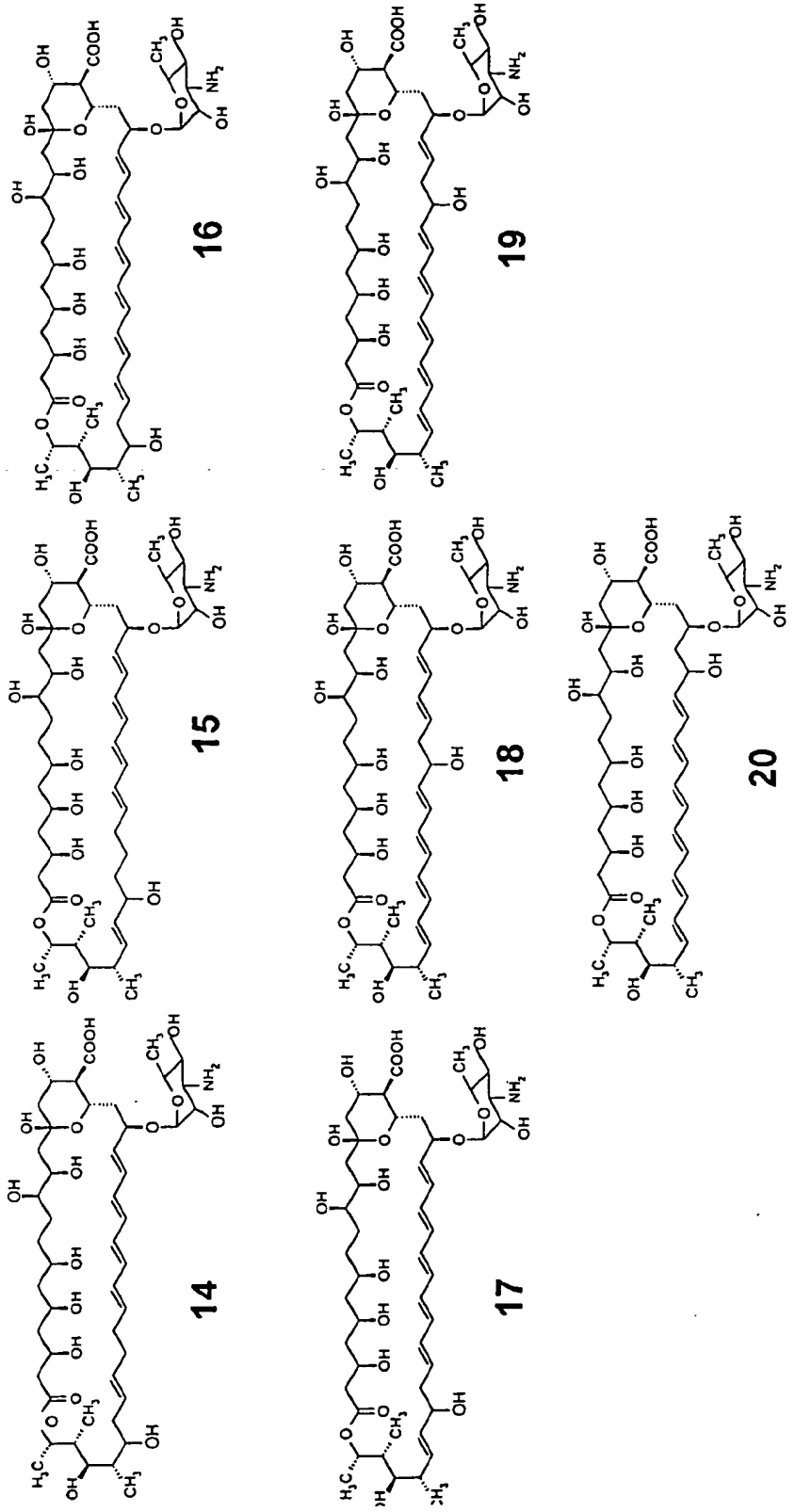

FIG. 12

SEQUENCE LISTING

SEQ ID NO. 1

DNA sequence: (Nysl; region 1)

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21151 cgaccgcggc tgggacgccg agggcctcta cgacccggac cccgaccggc
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22101 ccagcgtcat caagctcgtc cgcgccctcc aggaaggcgt ggtgcccaag
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22301 atcctcgaac aggcccccgc ggacgaggcg cccacgcccg ccgacccgcc
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23151 tcgccgacct cttcgccgcc gacgggcgcc ggaccaagcg gctgcgggtg
23201 agccatgcct tccactcgcc gctgatggac gccatgctcg acgacttcgc
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23351 tactgggtcg ggcacgtccg cgccgcggtc cgcttcgccg acggcatcga
23401 ctggctcgcc acccagggcg acgtccacac cttcctggag ctcggcccgg
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23551 ggtcaccgcg gtcgccgcgg cccacgcgca cggcgcccgc gtcgactgga
23601 gcgggtactt cgccgaccac ggcgcgcgcc ggaccacgct gccgacctac
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23701 ccacacgccc ggatccgccc tcgacgccga gttctgggcc gccgtcgagc
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24001 cgacgtcgag accgccctgg gcaccaccac cgtccggctg acggtcacca
24051 ccaccgaccg cgccgcgctg gccgcccgga tcaccgaagc cgccggcgac
24101 cagggcccgt tcagcggtgt gctgtccctg ctgccgctcg ccaccggcga
24151 cgccggccac cccggtgcgc ccgccgccct caccctcacc accaccgccg
24201 tccaggccct cggcgacgcc ggcatcgacg cgccgctgtg gaacgtcacc
24251 cgcggggccg tggccgtcgg ccgcgccgaa caggtcaccg cgcccgaaca
24301 ggccgccgtc tggggcctgg gccgcgccgt cgccctggaa ctgccggccc
24351 ggttcggcgg caccctcgac ctgcccgcca ccctggacgg ccaggccgcc
24401 cgccggttgc gcgcggtgct cgcggctacc gacggcgagg acgcggtggc
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24501 gccccgacac cgcccgcacc gccttcgacc cggcggccgg caccgtcctg
24551 atcaccggcg gcaccggcgg catcggcggc cacgtcgccc gccgcctggc
24601 ccgcgacggc gccacccacc tgctgctcac cagccgccgc ggcccggccg
24651 cccccggcgc cgacgcgctc cgcgccgaac tggaggaact gggcgcccgg
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24801 ccggcgtcgt cgaggaccac gtcgtggacg cgctcacacc ggagaacttc
24851 gccgcggtgc tgcgcgccaa gaccgtcgcc gcccaccacc tgcacgagct
24901 gaccgccgac ctggacctcg ccgctttcgt gctgttctcc tccacggccg

24951 gcgtcctcgg cgccgccgga cagggcaact acgccgcggc caacgcccac
25001 ctggacgccc tcgccgaaca ccgccgctcc cacggcctga ccgcgctgtc
25051 cgtcgcctgg ggcccgtggg ccggctccgg catggtcgcc gacgccgccg
25101 aactcaccga ccgggtacgg cgcggcggct tcgaaccgct cgccccccgaa
25151 ccggccgtgc gcgccctgct gcgcgccatc gagaacgacg acaccaccgt
25201 cgcgctcgcc gacatcgact gggagcgctt ccagcgcgcc ttcgccgcgg
25251 tccgcccgct gccgttcgtc gccgacctcc ccgagaccgg ccgggccacc
25301 cccgcgaccg ccaccggcgc cgccaccggc ctgcggcagc aactcgccga
25351 actgccggag cacgagcgcc cggcagcggt cctggacctg ctgcgtaccc
25401 aggtcgccgc cgtcctcggc cacgccgacc cgcgcaccgt cgaggacgac
25451 cacgccttcc gcgacctggg cttcgactcg ctgaccatcc tggaactgcg
25501 caacgccctc aacgccgcca ccggcctgag cctgcccgcc accctggtct
25551 acgacctgcc caccccgcgc gagatggcgg acttcctgct cgccgaactc
25601 ctcggcaccc tgcccaccga caccgccgcg accgtcgcca gcacggcctc
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25751 ccggaggagc tctggcagct cctcgacgag ggccgcgacg gcatcagccg
25801 cttccccgac gaccgcggct gggacctcgc cgcgctgggc gccggcgcct
25851 ccgacaccct ggagggcggc ttcctgaccg gcgtcgccga cttcgacgcc
25901 cggttcttcg gcatctcgcc ccgcgaggcg ctggccatgg acccccagca
25951 gcggctgctg ctggagacca cctgggaggc gctggagcgg gccggcatcg
26001 acccgaccac gctgcgcggc tccaccaccg gcgtcttcgt cggcaccaac
26051 ggccaggact acccgacgct gttgcgccgc tccgcctcgg acgtggccgg
26101 ctacgtcgcc accggcaaca ccgccagcgt gatgtccggc cgcctgtcct
26151 acgcgctcgg cctcgaaggc ccggccgtca ccatcgacac cgcctgctcc
26201 tcctcgctcg tcgccctgca ctgggccggc cgggcgctgc gcgccggcga
26251 gtgcgacctc gtggtggccg gcggcgtctc ggtcatggcc agcccggact
26301 ccttcgtcga gttctccacc cagggcggcc tggcacccga cgggcgctgc
26351 aaggcgttct ccgacgccgc cgacggcacc gcctggtccg aaggcgtcgg
26401 catcctcgtc ctggaacgcc tctccgccgc ccgccgcaac ggccaccagg
26451 tcctcggcct gatccgcggc accgccgtca accaggacgg cgcgtccaac
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26551 actcgccgac gcccgcctgc gccccgccga catcgacgcg atcgaggcgc
26601 acggcaccgg caccaccctc ggcgacccga tcgaggcccg cgccctgatc
26651 accgcctacg gccgggaccg ggacgccgaa cggccgctgc tgctgggcac
26701 cgtcaagtcc aacatcgggc acacccaggc cgccgccggt gccgccggcg
26751 tcatcaagat gctgatggcg atgcgccacg gcaccctgcc caggacgctg

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26801  cacgtgggca ccccgtccag ccacgtcgac tggagcggcg gcaccgtcgc
26851  gctcctcgac gacgcgcggc cctggccacg gaccgggcag ccgcggcgcg
26901  ccggcgtctc cgccttcggc gtcagcggca ccaacgccca cgtcgtcgtc
26951  gagcaggccc cggaaaccga agcccccgcc gccccggccg ccgagccggc
27001  gccggaggcc acgcccaccg tcgtcccctg ggtcgtctcc ggacgcagcc
27051  gggaagcgct ccaggcgcag ctggaccggc tcaccgcgca caccgccgcc
27101  caccccgcgc gctcggcggc ggacgtcggc cgctcgctgg ccaccgaccg
27151  cacgctcttc ccgcaccgcg ccgtgctgct cgccggcccg gacggggtgc
27201  gcgaggccgc ccgcgccgcc gcgccccgca cccccggccg caccgcgttc
27251  ctgttctccg gacagggcgc ccagcacgcc ctgatgggcc acgacctgta
27301  ccagcgcttc ccggtctacg ccgacgcact ggacaccgtc ctcgcccagt
27351  tcgacaccgt gctggacgtc ccgctgcgcg ccgcgctgtt cgccgcgccg
27401  ggcacccccg aggccgcgct cctggaccag accggcttca cccagcccgc
27451  gctgttcgcc gtcgaggtcg cactgttccg gctcgccgag tcctggcggc
27501  tgacgccgga cttcgtcgcc ggccactcca tcggcgagat c
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SEQ ID NO: 3

NysD2 (incomplete - probably C-terminally truncated).

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  1  msftypvsmp wlqgreldyv teavgggwis sqgpyvrrfe eafaayndvp
 51  fgvacssgtt altlalralg vgpgdevivp eftmiasawa vtytgatpvf
101  vdcgddlnid vsrieekitp rtkvimpvhi ygrqcdmdav lnlayeynlr
151  vvedsaeahg vrprgdiacf slfankiisa geggvclthd phlaeqmahl
201  ramaftkdhs flhkklaynf rmtnmqaava laqteqldti lalrrdiekr
251  ydealrdipg itlmpprdvl wmydlraerr delcaylage gietrvffkp
301  msrqpgyfsa dwpalnaarl sadgfylpth tgltaqeqef itgri
```

SEQ ID NO: 4

NysD1

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  1  vtlpsgntrl gwrrrrmhsp gdragrvrga rarrpatfrg vlsmganrrp
 51  ilfvsyaesg llnpllvlag elsrrdvadl wfatdekard evaavvdgsp
101  vrfaslgdtv sqmsavtwdd atyaevtqrs rfkahaavir hsfapesrma
151  kyrrleeive evepalmvie smcqfgyela itkgipfvlg vpfvpsnvlt
201  shvpfaksyt psgfpvphsg lpaamslaqr ienqlfrlrt lgmfltsdvr
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```
251  kvveednrvr telgiapqar qmmaridhae qvlcysvrel dypfpmhpkl
301  rlvgtmvppl pqapdddgls dwlsaqksvv ymgfgtitrl treqvaslve
351  varrldgrgh qvlwklprgq qellppaael pdnlriegwv psqldvlahp
401  nvkaffthag gngyheglyf gkplvvrplw vdcddqairg qdfgvsltld
451  rpetvdtedv ldkitrvldq psfteraehf agllrdaggr aaaadlllgl
501  palatd
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SEQ ID NO: 5

NysA

```
   1  mtigadedpv vvvgmacryp ggvagpedlw elvrtgrdat tafpddrgwd
  51  laalagdgpg rsatreggfl tgaadfdaaf fgmspreavs tdpqqrlvle
 101  tawealerag idphslrgsr tgvfvgasgq dyaavthasp ddldghaltg
 151  lapgvasgrl ayvlglegpa vtvdttssss lvalhwavra lragecstal
 201  aggvtvmstp aafvghtrqg glapdgrckp fsddadgtaw aegvgivvle
 251  hlstaraagn pvlavlrgsa vnqdgasdgl tapsgpaqer viraaladar
 301  lapadidlve ahgtgtrlgd pvearallaa ygqdrdpdrp lrlgslkstl
 351  ghaqaaagig gviktvltlr hglmprirhl atptrqvdws qgavapltdh
 401  tpwppadrpr ragvssfgis gtnahvilee appadvpvtr pgtlrpstvp
 451  wpvsaatpea ldaqlarlra hlrthsdldp ldvgyslatg raalrhravl
 501  lppadgtaad avehargaah qrrtavlfsg qgsqrpgmgr elaarfpvfa
 551  dalddalral drhldgpvre vmwgtdaall drtgwtqpal favevalhrl
 601  vaslgvtpdf vgghsvgeia aahvagvlsl edacrlvaar atlmqalpag
 651  gamaaleate devapllgah lalaavngpt avvvagaeda vrqltarfad
 701  rgrrtsrlav shafhsplme pmldafrdvv srltfhqpsi plvsnltgel
 751  agseitsaey wvrhvrdtvr fadgitalak agadvlielg pggvlsamar
 801  dtlgpdsttd vvpalskgrp eetafagalg rlhtlgvpvd wpafyagtga
 851  rrvelptyaf qhvrhwptpp rpngagpgal ghpllgsave ladgggtvcs
 901  galslrthpw ladhtvagrv vlpatallel avragdeagc dvlhelhltt
 951  ppalpddaal hvqvhvgpad ttgrravtvh trpdhhpagd wtrcatgtlg
1001  stppsaaeaa tggtpaawpp adaepldlad hyerladrgf dygptfrglr
1051  aawrrgaeif advecppgta ddapdhglhp alldaarhaa mavdgtvpva
1101  whgvrlhavg atalrvrirp tttgtltlta vdvhgapvvt vealtarplt
1151  deeraaprtp rqargetpad arparpaaar pgpageplpd ttgshptagh
1201  laalppaare rqlldlvrtq aaavlghpgp eavgtrsvfk elgfdslagv
1251  eladrltart glrlpatlvf nfptperaah rlgellaata pldpgaygee
```

1301 ltrfeaivtn lpqdgperra vadrldaivs alrqnspaev pssdedidtv
1351 svdrlldiid eefett

SEQ ID NO: 6

NysB

1 mqepqqgqpd qqekivdylr rvtsdlrrar rrigeleskd nepiaivgmg
51 crlpggvnsp eslwdlvrsg gdaisgfpvd rgwdletltg ngdgssathe
101 ggflydaaef daaffgispr eatamdpqqr lllevaweal eragiaptal
151 rgsrsgvfvg syhwgapsad aatelhghal tgtaasvlsg rlaytlgleg
201 pavtvdtacs sslvalhlaa qslrvgessl aviggvtilt epsvfvefsa
251 qgglapdgrc kafsdaadgt gwaegvgvlv aerlsdaqrn ghpvlavlrg
301 savnqdgasn gltapngpsq erviqqalar tgltpadida veahgtgtrl
351 gdpieaqall atygqghtpd qplwlgslks nightqaaag vagvikmvma
401 lrhghlpptl hadapsshvd wsagsvrllt egqqwpetgr prraavssfg
451 isgtnahall eqaphpadta dagddaapte pagapaalpw ivsghspqal
501 rdqaaalaar vetdpalrpq dightlhtar allerravvv apdraellaa
551 thelaagrsa navvegladv egrtvfvfpg qgsqwvgmga qlldesavfa
601 eriaecaaal aeftdwslvd vlrgvvgaps lervdvvqpa sfavmvslaa
651 lwgsrgvlpd avvghsqgei aaavvsgals lrdgarvval rsqaigrala
701 grggmmsval svdvleprlv efegrvsvaa vngprsvvva gepealdalh
751 arltaddira rriavdyash shqvedlhee llevlaelap rtsevpffst
801 vtgdwldtar mdagywfrnl rgrvrfadav adllaaeyra fvevsshpvl
851 tmavldliee agvtavatgt lrrdqggagr fllsaaevfv rgvdvdwaga
901 fegtgaarvd lptyafqrer ywntrtaadr tpadapmdae fwaaveqadv
951 saltaalgtd edsvaailpg ltswrrarsq rttldswryr vtwtplaqvp
1001 ratltgtwll vttdgiddtd vagalesyga evrrlvldee ctdravlrer
1051 lagaedvtgi vsvlaaaedd aarhpgltrg laltvslvqa lgdaeatapl
1101 wfltrgafat gpsdpvtrpl qsqiagvgwt talehpqrwg gtvdlpdtld
1151 araaqrlaaa lsgalgaedq lavraagvla rrivraghra grpartwapr
1201 gttlitggsg tlapqlarwl aergaehvvl vsrrgadapg apeliaeaae
1251 sgtevtvaac ditdrdavaa lladltadgr tlrtvihaaa aielsaladt
1301 tvaefadvvh akvtgarild ellddaeldd fvlysstagm wgsgvhaayv
1351 agnaylsala eqrrarglrt tsihwgkwpd drareladph rirrsgleyl
1401 dpelaltalq hvldddetvi glmdidwdty hdvftagrpa hlfdqipevr
1451 rrldqasvpd pagpaadgla arlhglaaae qdrllltlvr teaaavlgha

1501 saesfperra frdlgfdsvt avdlrnrlva gtglrlpstm vfdhpncaal
1551 aaflkttalg vpgaapqqha atgtpadddp iavigmscry pggaatpeel
1601 lrlaldgadv isefpadrgw darglydpdp drpghtysvq ggflheaagf
1651 dpgffgispr eavamdpqqr llletsweaf eragidpasl rgsaagtffg
1701 asyqdysstv qngtgeseah mvtgtaasvl sgrvsyllgl egpavtvdta
1751 cssslvalhl acqslrdges slalaggaav matphafvgf srqralakdg
1801 rckpfsdtad gmtlaegvgv vllerlshar anghrvlavi rgsavnqdga
1851 sngltapngp sqqrvirqal anagltgadv daveahgtgt klgdpieaqa
1901 llatygqdrd aerplllgsv ksnightqaa agvagvikmv lamdagelpg
1951 tlhldapssh vdwtagavel lrgrtpwpes grprragvss fgisgtnahl
2001 ileqapatep padpdrlrdt atdtvvpwpl aakspaalra qaarllatve
2051 hdpdlppapv ghalattraa lehravvvge rredflrgla alstgastag
2101 lvsgiagpdp egavfvfpgq gsqwwgmgre llatsevfrt aiddcatala
2151 pyvdwslhdv lagegdpall ervdvvqpal fammvglsal wrshgvvpaa
2201 vvghsqgeia aacvagalsl adaarvvalr sqalpqlsgr ggmmsvsapv
2251 ervtallapw qealsvaavn gpssvvvsgd tdaldalhta cqeqgvrark
2301 vsvdyashgr hveavrdela rvlapvdpra pevpfystvt gdrvddaafd
2351 gaywytnlrq tvrmeeatra llaaghrvfi evsphpvlaa piqetqeava
2401 eatggsavvl gslrrdeggp rrfltslaea hthgapvdwt ttfarsayqp
2451 vdlptypfqr qdfwpearpa tpaagadasd aafwqlvenq dlaaladalg
2501 vpaddehtal gtvlpalsaw rakaqartri delryhvqwt rvaepaaapt
2551 tgrllvavpp dhadapwvaa aldalgtdtv rfeakgtdra gwaaqiaqlv
2601 edgeeftgvv sllaaaedlh pdfgsvplgl gqtlvlvqal gdagltaplw
2651 cltrgavatg rddaldsptq galwglgrvv alehpdrwgg lidlpatlda
2701 raaarltgll adpagedqla vratgvlarr mvhaapsapr tgrrwrgrgt
2751 clitggtggi ggrvarwmae hgaahlvlts rrgpdapgaa alraelealg
2801 arvtlaacdv adrdalaall adlpadqplt svfhsagvad gdaraadltl
2851 dqldallrak ltaahhlhel tapldldafv lfssgaavwg sggqpgyaaa
2901 nayldalaah rrsldlpgas vawgtwgevg matvpevher lhrqgvrame
2951 pdhaigalqq mledddttla vtlmdweafa psftatrpsa lfstvpeavr
3001 avtgdpgtta gddvdsatpp lrrhleelsa aergralvea vraeasatlg
3051 hdtpdaipag rafrdvgfds vtavelrnrl rtalglplpa alvfdhptpt
3101 alaghlgall fgtapedagt grpddpdari realatvpig rlrkaglldm
3151 vlkladgdat dapapeadap seslddmdae allrlatens an

SEQ ID NO: 7

NysC

```
     1 mstnpdkyve alrsslkeie rlrrqneqlv aaavepvavv gigcrfpggv
    51 tspedlwelv aegrdvigpf pqdrgwdlek lagggeggsl aqvggfveda
   101 agfdpgffgi spreavamdp qqrilleitw ealeragidp stlrgtptgv
   151 fvgttgqdyg evikasaedv evysttghaa svisgrlsyt lgaegpavtv
   201 dtgcssslva lhwavqalrg gecsmalagg asimatpgpf vaftaqsgla
   251 adgrckpfsd radgtgwgeg agmlvlmrls daqregrpvl avlrgsainq
   301 dgasngltap ngpsqqrvir aaldsahlta adidaveahg tgttlgdpie
   351 aqallatygq drprplwlgs vksnightqa asgaagvikm imalqrgvlp
   401 rslhateptt dvdwtagsvd lldetvawpe tgrarragvs sfgisgtnah
   451 vileqaptap eeptteptvr pavvpwalsa rtaaaldaqr arltghladt
   501 pdadpldvgy aladgratfe hravllpdgt elahgtageg pcavlfsgqg
   551 sqrpgmgrel harfpvfaaa fdeitalldt hldrplrevv wgtdadllnd
   601 tgwaqpalfa vevalyrlva slgvtpdfvg ghsigelaaa hvagvlsled
   651 actlvaarar lmqalprgga mlairatede vtphltddvs iaavngptsv
   701 vvagteeava aigarftaqd rkttrlrvsh afhsplmdpm laefravaag
   751 ltyhepripv lsnltgtvaa vadlcsadyw vrhvreavrf adgvtaltdr
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SEQ ID NO. 8

NysE

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SEQ ID NO. 9

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401 lrdaaaqaes rgapeagvrc lyrvlevepd nvavriqmar alaeinppea
451 mrllkealsl agdvrtraqv avqygftcla vqespsgvrm ledalaelta
501 elgpepgpvd relrtlvesv llivgadekv tigavrdraa rltmppgdtp
551 aqrqmlamtt vltamdgrda rsavdqarra lrapgvelep wsllsasfal
601 sladevadaq yaldlmlqyg qdnaavwtyv lalstrallh hgvgafpeal
651 adaqtaveil geerwadgav lprvalatal vdrgeperae hvldgitrpr
701 lerfvieyhw ylqarayarw vrgdfqgald lllacgrsle esrfsnpafv
751 pwwadgavll atldrhdqar elaaygsela erwgtarglg lafmaqgvaa

801 pgragidhlt eavslladsp aramearael llghahlkrd dlraarehlr
851 aaadlaqrcg avklgvdark llvtaggrvr rmtaspldml tgmertvadl
901 avtgasnrai aealfvtvrt iethltsvyr klgvggrael savletrtat
951 sgrqppawvs qargra

SEQ ID NO. 10

NysR2

1 vprskarnqp ttctpqcapd ahgdptmlle cgreqrligd llhrlgqgrp
51 svlsltgrpg haqnalvrwg acrarhdglr vlraqatpae relrygavlq
101 llavldgphg stldaairhd gppplpvpgi eevlrrtgta ptlvvvedvq
151 wldpasltwl qillrhlgpd tplavlassc gdttafdtdp kapavpgppd
201 tvpvarfvvp altdrgvaat vravcgtpgd eefiaaltsa tagnpailrd
251 alrafvdhgl padadhlpel haltagvvgd htvraldglp aevnavlral
301 avcgdlldfh rvralagahs lsedrirtll asvgltvsvg dkvhirfpas
351 karviedmpa aeradlyvra aelthscgvn dedvahlllr ssplgapwvv
401 pllrrgfaaa lrredhhrac aclsralqep ldprersllt lelaaaeava
451 rpeagdrrlg elvrstvadt dptssgegvg vraidlgfar gnsewvrrta
501 gealpyagpa dreelvalfw laavrdddap mipvvprlpd rpvppaqaga
551 rawqlatage dadkarklar ialtggvnes lmmpklaaca alfatddnde
601 avhgldtmlt aarsahlrsm aarifnlrar ihlcaarlea aerdldsaer
651 alpptswhpr alpnliatri lvsmetgrpd rarrlaeapv paggeegvww
701 palllararv aaddgdweea lrlsrecgrw lfrrhwanpa mlswrplaae
751 aclklgdvte arrlrdeelf fadrwgtasa rgiarlttrr lfdddgdrav
801 rrireaaall rdsparlayl wsrlsqagae tahgdtaaaa rswqavarmt
851 aahpasrlat aartltvpsv pvatapptav vppgwrdlse aekdtvllaa
901 rghgnrqiae qlavsrrtve lrlsnayrkl riggrkelyl llealegpva
951 das

SEQ ID NO. 11

NysR3

1 mllerenela riraaldaae agdsslllin gplgsgrsal lrripelagd
51 gtrvlrasaa wrerdfpfgi arqlfdhlls gaggagpaer tagaehfsrl
101 mdtgdrptgt gpalevsqav lqgaqallad asaerrllil vddlqwadgp

151 slrwlahltr rlhglrallv ctladgdhrg ryplvrevag aahtvlrlap
201 lsrdatrvll agpqgrppqd alvravyeas rgnplfltaf rsalratgrp
251 pggdhfgavr elsptvlrdr laghlriqpq pvrevavava algdhsdpvl
301 laqlagvdei gfagarralv dagllargrd vrfvhgvvrd avdsllt1de
351 rershddaad llyrcgrpae qvaghllavv hpgrpwseav lrsaahnalr
401 agrpadaary lrrallhhrt qdgcrarilv dlataerald pdacvrhvsq
451 avalldtsrd raaavlripp sllaapspsa velvrqaaag ldepgqrdee
501 gadelalrle awlrhsghen pvelassvar lrrmgarppv dsvaerelva
551 vllsagalsg rlsaaeiadt gnrilerepa taahahtplp lvmlslfvae
601 svqgvaswla seqhtrrrya tgaddvllta erafvlvtqg rpaaarehve
651 ralvmdagdw sepavmmfaa vafelrdpal serilerird rrpaglalta
701 tgqmlqaavd vhfgrgrdal dtllacgrrl etvgwrnsal lpwrpyaigl
751 hqrlgetdaa lqlaedelrw arewgattnl gralrlkgwl lqdegldllr
801 esveilrass yatelartlv vlgrrlpggp eaeavlreaa giaaacgvpw
851 laeraelglg saivppvatl tpserrvasl vsrgltnqai atelgvssra
901 vekhltsayr klgvsgrrel vnalpgr

SEQ ID NO. 12

NysR4

1 visaqtapag esvgpglmas ldrdltikha nqefrrrfdd sagdvcgrsf
51 rdlmhpsvqq plmrqfsrli egkrhrfash vvavgaqdaa fagtltasav
101 tgktpdiagi lvlmdssgaa daadagvvts qkkflteida rilegiaagl
151 stiplasrly lsrqgveyhv tgllrklrvp nraalvsray smgilnvgtw
201 ppkvvddfik

SEQ ID NO. 13

NysR5

1 vdaegrrrdm lelirrsgsa dvvrlaeefa vsketvrrdl nvleghglir
51 rrhggaypmv rpgseavfvs rtaqpipees riataaaell seaetvfide
101 gftpqliada lprdrpltiv taslpvvsaf atspqanvll lggrvrrgtt
151 atvdhwavhm lsgfvidlaf lgaegisrry glttpdpava evkaqairva
201 rrpvlagvht kfgtasfcrf gevgdletiv tgaglpvaea hryhlmgpkv
251 lrv

SEQ ID NO. 14

ORF2

```
  1 vaqdsgqtpr sldhvdqalv halqitpras wtrigsvlgl davtvarrwn
 51 rlvetgaawi schpapvlaa sgqgclafve idcapgrlld varalaaaph
101 vvalshvtgd rdlqlnvmar dpamlsrwvt hdlaaldgvr aarthlagpv
151 htegsrwrlr algrhqvarl aadasrhrtd tpafvldeld qqlvtalsvd
201 gratyralae qcgagpdtvr rrvqrlfaad mlharcevar plsewpvtvs
251 fwgqvpaarl revtrrvtgm revrlcasvi srhnlhlvaw vrslddaqrf
301 evrlaeraad ltvteraval whmkhgghll deegyrvgvt plalwreptd
351 arrg
```

SEQ ID NO. 15

ORF1

```
  1 mqpelerlrr slhrepelgl alprtqekvl aaldglplei tpgtgltsvt
 51 avlrggrpgg avllrgdmda lpvteesgvp yaseipgrmh acghdlhtag
101 lvgaarllae rrerlhgdvv fmfqpgeegh ngagamieeg vldaagkpld
151 aayalhvasn qvpggvvitr sgtitsasdl ltvtvrgegg hgstpatakd
201 pvpaacemvt avqnwvtraf difdpvvvtv gtfhagtkas vipdnrrvpg
251 hgaqlfrirp gparrrelpr lvraiaaahg leaevdylrh ypvtvndtde
301 tafavatard lfapgevwes piptngsedf ayvlrrvpga mllvgaapeg
351 sdwqhapmnh spravfddrv lyrqaallte laarrlaata paepavag
```

Translation products of SEQ ID No. 2 (Nys 2):

SEQ ID NO. 16

NysF

```
  1 vielilpatv ateaayddrp rpgdrllsse reviaraves rqrefttvrh
 51 larralrrlg hpdrailpnr rgapqwppgi vgsmthcagy raaavspael
101 saavsidaep ngplpagvln aialpserph lvalaahrpd vhwdrllfsa
151 kesvfkawyp ltqreldfse aeividptqg aftarllvpg pllggrrvtv
201 fpgrwhstpa llttavhlpa ptprrdrehr thltvnsplp rptfg
```

SEQ ID NO. 17

NysG

```
  1 maspddleee rtaprparrl vgllrphrrs valavsmgvg givlnafgpl
 51 llgrvtdlia dgvlggvpgp apgidfaaig rlllvllaly vvaslfmlaq
101 grlvasavwr tihelrrdar ekltrlplrh fdrqpagell srttndidnl
151 qqtlqqtlae litsifsllt mlvlmlvisp slavvmllsv pvsaliaari
201 skraqphyaa qwsangtlna hveevctgha likgfdrraa aeerfdacnd
251 avyraaakaq fasgamepvm mfvanlgyvl vavigawkvi ngtltlgdvq
301 afilyarqfs qpiveiasva grlqsgiasa qrvftlldap eqapdplrpg
351 tparaegrve ftdvsfrysp dtplienlsl tvepgstvai vgptgagktt
401 lgnllmrfye pdsgrilldg tdtatmtrdd lrsrfglvlq dtwlfggtia
451 eniaygapga cradieeaar atcadrfirt lpqgydtvld desgtvsage
501 kqlltvaraf larpavlvld eatssvdtrt evliqramns lragrtsfvi
551 ahrlstirda dlivvmdagr iveqgthdql lcaqglyarl haarthtpta
601 gaaag
```

SEQ ID NO. 18

NysH

```
  1 vllrllraql rpyawataal valqlvqilg tlllptlgaa lidqgvvrgd
 51 ggritelgvv mgvvalvqia aalgaaalaa rtatamgrdl rsalfrrild
101 fsareigrfg tpslltrsvn dvqqvqnlaq tgfgivvcap lmclgsvlla
151 lrqdvplall lvalvlvvav cfglllarmg tlyarmqltl drlgrllrea
201 itgvrvvrsf vrddherarf aqtndaflvv srrvgrliat mlpvvlllmn
251 gftvallwtg shridagrmp igslsallsy lslilmsvvm lafvflsvpr
301 arvcagriae vldtgssvap paapqpvrgp agrielcaag yrypgaeepv
351 lrdvdltvep geriavlgst gsgkttllnl vlrladateg avrvggtdvr
401 eltaatlaaa vgfvpqrpyl fsgtvasnlr fgrpdatdee lwealrvaqa
451 adfvarmpdg ldaeitqggg nvsggqrqrl slarallrrp eiylfddcfs
501 aldqatdaal rtalvpytag atvitvaqri sagrdadriv vldrgrvvaq
551 gthdvllrts ptyreialsq lteeeaahgl agrp
```

SEQ ID NO. 19

NysD3

```
  1 mskralitgi tgqdgsylae hllsqgyqvw glirgqanpr ksrvsrlase
 51 ldfidgdlmd qgslvsavdt vqpdevynlg aisfvpmswq qaelvtevng
101 mgvlrmleai rmvsglstsr tvsprgqirf yqasssemfg kaaetpqret
151 tlfhprspyg aakayghyit rnyresfgmy avsgmlfnhe sprrgqefvt
201 rkislavari kqglqdklal gnldavrdwg yagdyvramh lmlqqdagdd
251 yvigtgqmhs vrdavriafe hvglnwedyv vidpdlvrpa evevlcadsa
301 kaqdrlgwkp dvdfptlmrm mvdsdlaqvs renqygdvll aanw
```

SEQ ID NO. 20

NysI aa sequence (partial)

```
  1 mdneqklrdy lklatadlrr trrrvhkles aaqepvaiig mtcrypggvr
 51 spedlwrmve agehgvtpfp tdrgwdleal aaaptasggf lhdapdfdad
101 ffgispreav amdpqqrvvl esaweafera gidptsvkgs rtgvfigama
151 qdyrvgpadg aegfqltgnt gsvlsgrisy tfgtvgpavt vdtacssslv
201 avhlatqalr agectlalag gvtimsgpgt fiemgrqggl sadgrcrsfg
251 dtadgtgwae gvgilvlerl sdavrnghei lavvrgtavn qdgasnglta
301 pngpsqqqvi qqalvnarla agdidvveah gtgttlgdpv eaqallatyg
351 qnrpadrpll lgsvksnlsh tqaaagvagv ikmvmamrhg tlprtlhaee
401 pthhvdwsqg avrlltdttd wpatgaprra avssfgisgt nahtiieqap
451 epqpedaata qddaagstpa tapvvpgvvp vllsgrtpda lrgqaaalra
501 aldtgrrpdl ldlahslatt ragfehravl latdhpaltd gltaladadd
551 paaapawitg ttraetrlav lftgqgaqrl gagrelaarf pafataldaa
601 ldaftphldr plrevlwgtd aalldrtaya qpalfaveva lyrliesfgv
651 rpdhlaghsv geivaahlag vlsladaatl vaargrlmqa lpdggamiav
701 qaseadvapl laghedqvai aavngpsavv lsgaeatvta laeqlaadgr
751 ktrrlrvsha fhsplmepml dafravvedl tlqppllpvv snltgkpatv
801 aqltsadywv dhvrhavrfa dgidwlarhd ttaflelgpd gvlsamaqdc
851 ldaadadavt lpalragrpe ehtlttalag lhvhgatldw tgcfagtgar
901 rtdlptyafq rrrywpkalq sgtadlrsvg lgaahhplls aavsladagg
951 tlltgrlsrq thpwladhtv rgttllpgta flelavragd evgcdrveel
```

1001 tlaaplllpe qggvqvqlwi gnpdvsgrrt vnvharpdtg ddtpwtahat
1051 gvlttadasr qlpasseqgg tplagdphpa ldaaqwppag aeplpldghy
1101 drladggfgy gpvfqglraa wrggdvvyae velpeagrsd aeafglhpal
1151 ldaalhaapf tglgergrgg lpfswegvsl haggattlrv rltpvaddal
1201 altvadgtga pvlsvdslvl rsvatqqldt aaavardalf rldwtpvqpt
1251 atdpgpvall gadpfgllth agfadapayp dlaalaaadg pvpttvvlsl
1301 agtgddaadp arsahrcaae alaavqtwld hherfaaarl vfvtrgatvg
1351 rdvaaaavwg lvrsaqsenp gcfalvdldp dgavgaaalv aalvsgepql
1401 avrgdvlrva rlvrrpltev gagadgtgdg vgdgsgvsfs gegavlvtgg
1451 tgglgavlar hlvaeygvrd lllvsrsger avgagelvae lagvgarvrv
1501 vacdvtdraa vvelvgghav savvhaagvl ddgmvgaltg erlsavlrpk
1551 vdavwhlhea trgldldafv vfsslagvfg spgqanyaaa nafldalmtr
1601 rraeglpgls lawgpweqsg gmtgtltdvd aerlarsgvp plsvaqglal
1651 fdaavagtda tcvpvrldlp vlrargevpp llrslirvra rraavagsat
1701 agnlaqrlrr ldedgrdemv ldlvrgqval vlghatggdv dagrafrdlg
1751 fdsltavelr nrlntvtglr lpatlvfdyp tvrhlatyvl dellgtdaev
1801 atvqpaavav addpivivgm acrypggvss pedlwrvlte gtdavsgfpt
1851 nrgwdvesly hpdpdhpgts ytrsggflhe agefdpgffg mspprealatd
1901 sqqrllless weaieragid pvslrgsrtg vfagvmysdy samlaspefe
1951 gfqgsgssps lasgrvaytl glegpavtvd tacssslvam hwamqalrsg
2001 ecglalaggv tvmstpavfv dfarqrglsp dgrckafada adgvgwsegv
2051 gvlvlerqsd avrngheila vvrgsavnqd gasngltapn gpsqqrvirq
2101 alasggltag dvdvveahgt gttlgdpiea qallatygrd reperplllg
2151 svksnlghtq aaagvagvik mvlamrhgvv prtlhvdaps shvdwsegav
2201 ellseqaawp etgrvrragv ssfgisgtnv hviveqapga kaiaaagaar
2251 rtpgavpvll sgrgrsalrg qaarllghlq arpdaelvdv alslattrsr
2301 feqraavvaq drdqliaslg alaadrpdpa vvegeaagrg rtavlftgqg
2351 sqraamgrel hevqpefaaa fdavcavfdp lldrplrevv faedgsdeaa
2401 lldetgwtqp alfavevalf rlveswgvrp dfvaghsige iaaahvagvl
2451 tledacrlva aratlmqalp tggamiaiqa tedeiaahld dtvaiaavng
2501 pqsvvisgde eaaetiaatf aergrktkrl rvshafhspr mdgmldafri
2551 vaegltyrap riplvsdltg rraddaevct aeywvrhvre avrfadcvrt
2601 lrdagattfl elgsdgllta maedtlgddh daelvpmlra graeelaaat
2651 alarlqvrgv dvdwaaylag tgarrtdlpt yafqhayywp qlptpaaala
2701 aadpadqqlw aavergdare ladilglgeq dltpldsllp altswrrgnq
2751 ekhlldtlry rvewtrlskp tapvldgtwl lvasdataad qpalldglad
2801 algshgarvr rllldd scad ravlaerlar tadvdaatqv lsvlplderd

2851 addcppltrg laltvalvqa ladtgaqgrl wtatrgavst npadpvthpv
2901 qaaawglgrg valehprlwg glvdlpqvfd eragqrlagi lavkdapdge
2951 dqvalratgv sgrrlvrhtv ealptaaeft atgtvlitgg tgglgaevar
3001 wlaragaqhl vltsrrgpda pgaaelrael egygpsvsvv acdvadrdal
3051 aavltalpee lpltgvvhta gvghygpldt lstaefaglt aaklagaahl
3101 dalladreld ffvlfgsiag vwgsgnqsay gaanayldal alhrrargla
3151 atsvawgpwa eagmaaddav setlrrqglg lldpapamte lrravvrqdv
3201 tvtvadvdwq ryaplftsar psaliaglpe vralaadert eqdatgasev
3251 vtrvralaep eqlrlltdlv rtesatvlgh ssadavpegr afrdvgfdsl
3301 tavelrkrlg aatglslpst mvfdyptple laqylraeil gavlevagpv
3351 atggaddepi aiigmacrfp ggvsspeqlw dlvasgtdai sefpvnrgwq
3401 tghlfdpdpd rpgttystqg gflheadefd ptffgispre alvmdpqqrl
3451 llettwesfe ragirpetlr stltgtfvgs syqeyglgag dgteghmvtg
3501 sspsvlsgrl syvfglegpa vtvdtacsss lvalhlacqs lrngesnlav
3551 aggatimttp npfiafsrqr alakdgrcka fsddadgmtl aegvgvvlve
3601 rlsdaqrngh pvlavlrgsa inqdgasngl tapngpsqqr virqalanar
3651 lapgdidale ahgtgtplgd pieaqalfat ygrdrdpesa lllgsvksni
3701 ghtqsaagia svikmvmalr hselpptlha dapsshvdws agtvrlltqa
3751 rawpetgrpr raavssfgis gtnahvlleq apvadtpaee rpavapvpia
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4001 lrdgarvval rsqaigrala grggmmsval svdvleprlv efegrvsvaa
4051 vngprsvvva gepealdalh arltaddira rriavdyash shqvedlhee
4101 llevlaelap rtsevpffst vtgdwldtar mdagywfrnl rgrvrfadav
4151 adllaaeyra fvevsshpvl smavqeaide agvpavaagt lrrdqggtdr
4201 fllsaaevfv rgvdvdwagl fegtgasrid lptyafqheh lwavppapea
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4301 rstvdawryr vawkplggtl phpsltgtwl lvtadgiddt dvagaletyg
4351 aevrrlvlde ecvdravlre rlagaedvtg ivsvlaaaer tdavpgtslv
4401 lgtaltvali qalgdaeida pvwaltrgav stgradelta pvqaqvtgig
4451 wtaalehpqr wggtldlpaa ldaraaqrla avlsgalgsd dqlairpsgv
4501 ftrrivraea tagrpagtwt prgttlvtgg sgtlaphlar wlaqrgaehl
4551 vlisrrgtaa pgaaelvael aesgteatva acditdrdav aalladlkad
4601 grtvrtvvht aatielhtld attladfdrv lhakvtgaqv laellddeel
4651 ddfvlyssta gmwgsgahaa yvagnaylaa laehrrangl palslswgiw

4701 addlklgrvd pqmirrsgle fmdpqlalsg lqralddnen vlavadvdwe
4751 tyhpvytsgr ptplfdevpe vrrltaaaeq sagtvaegef aaalralsda
4801 eqqrtlletv rteaasvlgl ssaedltdqr afrdvgfdsl tavglrnrla
4851 svtgltlpst mvfdypnpaa laaylhgela garsaaagaa avptgapdad
4901 dpiaivgmsc rypggvgsae dlwrialdev daisgfpadr gwdaeglydp
4951 dpdrpgrtys vqggflrdva efdpgffgis prealsmdpq qrllletawe
5001 afehagidpv gqrgsrtgtf vgasyqdyas gvpnsegseg hmitgtlssv
5051 lsgrvsylfg fegpavtldt acssslvamh lacqslrnge sslalaggvs
5101 imstpmsfvg fsrqralaed grckayadga dgmtlaegvg lvllerlsda
5151 ranghqvlav irgsavnqdg asngltapng psqqrvirqa lansavapgd
5201 idvleghgtg talgdpieaq allatygqdr aperplllgs vksnightqm
5251 asgvasvikl vralqegvvp kslhidrpst hvdwssgaig lltertpwpe
5301 tgrprraavs sfgisgtnvh tileqapade aptpadpprd glvpvllsgr
5351 geaalraqaa rllafveerp eahltdlahs latsraaler raaviaadrd
5401 tltrglrals dgrpdpglvq gtagrgrtaf lftgqgsqrp gmgrelhdry
5451 pvfadaldev larlddgpdr plrevlfaap dsaeaalldr tgyaqpalfa
5501 vevalfrllt swgltpdyla ghsvgelaaa hvagvlsldd actlvaargr
5551 lmqalpegga mvaleaaede vlplllegltd rvsvaavngp rsvvvagvee
5601 dvllladlfa adgrrtkrlr vshafhsplm damlddfaav argltyhppt
5651 ipfvsnvsgg lataeqvrtp dywvghvraa vrfadgidwl atqgdvhtfl
5701 elgpdgvlsa maresltdps rtallptlrg drpeepalvt avaaahahga
5751 rvdwsgyfad hgarrttlpt yafqrerywp dttaatsaht pgsaldaefw
5801 aaverddvaa laasldldda tvtamvpalt awrrrrgeqt eldswryrvt
5851 wkprggatap aaltgrwlvl vphdhqdrqd dataawaadv etalgtttvr
5901 ltvtttdraa laariteaag dqgpfsgvls llplatgdag hpgapaaltl
5951 tttavqalgd agidaplwnv trgavavgra eqvtapeqaa vwglgraval
6001 elparfggtl dlpatldgqa arrlravlaa tdgedavalr psgvflrrla
6051 hapagpdtar tafdpaagtv litggtggig ghvarrlard gathllltsr
6101 rgpaapgada lraeleelga rvtlaacdaa drdalaalla elpddaplca
6151 vfhtagvved hvvdaltpen faavlraktv aahhlhelta dldlaafvlf
6201 sstagvlgaa gqgnyaaana hldalaehrr shgltalsva wgpwagsgmv
6251 adaaeltdrv rrggfeplap epavrallra ienddttval adidwerfqr
6301 afaavrplpf vadlpetgra tpatatgaat glrqqlaelp eherpaavld
6351 llrtqvaavl ghadprtved dhafrdlgfd sltilelrna lnaatglslp
6401 atlvydlptp remadfllae llgtlptdta atvastaspk lsasfeqggt
6451 pfddpiavig igcrfpggvt tpeelwqlld egrdgisrfp ddrgwdlaal
6501 gagasdtleg gfltgvadfd arffgispre alamdpqqrl llettweale

6551 ragidpttlr gsttgvfvgt ngqdyptllr rsasdvagyv atgntasvms
6601 grlsyalgle gpavtidtac ssslvalhwa gralragecd lvvaggvsvm
6651 aspdsfvefs tqgglapdgr ckafsdaadg tawsegvgil vlerlsaarr
6701 nghqvlglir gtavnqdgas ngltapngls qqrviaqala darlrpadid
6751 aieahgtgtt lgdpiearal itaygrdrda erplllgtvk snightqaaa
6801 gaagvikmlm amrhgtlprt lhvgtpsshv dwsggtvall ddarpwprtg
6851 qprragvsaf gvsgtnahvv veqapeteap aapaaepape atptvvpwvv
6901 sgrsrealqa qldrltahta ahparsaadv grslatdrtl fphravllag
6951 pdgvreaara aaprtpgrta flfsgqgaqh almghdlyqr fpvyadaldt
7001 vlaqfdtvld vplraalfaa pgtpeaalld qtgftqpalf avevalfrla
7051 eswrltpdfv aghsigei

SEQ ID NO: 21

Glu(Asp)Leu Gly Phe(Leu, Val) Asp Ser Leu

SEQ ID NO. 22

GAG/C CTG/C GGC/G T/CTG/C GAC TCC/G CTG/C

SEQ ID NO. 23

Val Asp Thr Ala Cys Ser Ser

SEQ ID NO. 24

G/CGA G/CGA G/ACA/ G/CGC C/GGT GTC G/CAC

SEQ ID NO. 25

GTTGGTACCCCACTCCCGGTCCGCAC

SEQ ID NO. 26

CCAGCCGCATGCACCACC

SEQ ID NO. 27

CCG CGT CGG ATC CGC CGA C

SEQ ID NO. 28

AGC CTT CGA ATT CGG CGC C

SEQ ID NO: 29

DNA sequence of ERD48.seq

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   1  gatccgccga cgacaccggc cgccgcaccg tcaccgtcca cgcccgcccc
  51  gacgacaccg ccgaccgcac ctggacgctg cacgccaccg gtgtgctcgc
 101  caccacgcca ccggccgccg cggcgttcga caccacggtc tggccgcccg
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 901  cccacggagc cgtcgccacc gacgacgcgc cccccaccga cctggccgcc
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1151  cacgccgtgg tccgcggacg gaacggtgtt ggtgacgggt ggtacgggtg
1201  gtctgggtgg gttggtggcc cggcatctgg tgcggtcgtg tggggtgcgg
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2601  gagcgggccg gcatcgaccc gctgaccctg cgcgacagcc gcaccggcgt
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SEQ ID NO: 30

Translation product of SEQ ID NO. 29 (ERD48.seq)

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 51  daeplttddc yahftthrfa ygpafqglra awragdvlya evalpesatd
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151 apngpnglsv taadpagnpv atvtrllarp ldaeqltihs altrdalfhl
201 dwtpvplpdt ansappallg pdtavladal gdpavarhat lddllagdtt
251 ppatvlvplg apldgdtaqh ahaltrsalt lvqqwlatdr ladsrlvfvt
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SEQ ID NO. 31

CGCCGCATGCTGTTCTCACCCCACGT

SEQ ID NO. 32

GGCGCGACCCGGTTCGGCCT

SEQ ID NO. 33

GCGAGCGGCCGCTTCACCCCGCAACTCA

SEQ ID NO. 34

CGCGAAGCTTGGCCGACTGCTCGACGTC

SEQ ID NO. 35

DNA sequence - 125401 bps (entire cluster):

1 gaattcggat cgatgctgct cgtggtgtgt gccgcgggag gtgccgacgg

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124651  tcaccgcggt gcagaactgg gtgacccgcg ccttcgacat cttcgacccg
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124851  gcggccgccc acggcctgga agcggaggtc gactacctcc ggcactatcc
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125101  accactcgcc gcgcgccgtc ttcgacgacc gggtgctgta ccggcaggcg
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125401  t
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SEQ ID NO. 36

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101  vdcgddlnid vsrieekitp rtkvimpvhi ygrqcdmdav lnlayeynlr
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151 vvedsaeahg vrprgdiacf slfankiisa geggvclthd phlaeqmahl
201 ramaftkdhs flhkklaynf rmtnmqaava laqteqldti lalrrdiekr
251 ydealrdipg itlmpprdvl wmydlraerr delcaylage gietrvffkp
301 msrqpgyfsa dwpalnaarl sadgfylpth tgltaqeqef itgrirafyg
351 va

SEQ ID NO. 37

NysI

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6801 gaagvikmlm amrhgtlprt lhvgtpsshv dwsggtvall ddarpwprtg
6851 qprragvsaf gvsgtnahvv veqapeteap aapaaepape atptvvpwvv

6901 sgrsrealqa qldrltahta ahparsaadv grslatdrtl fphravllag
6951 pdgvreaara aaprtpgrta flfsgqgaqh almghdlyqr fpvyadaldt
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7051 eswrltpdfv aghsigeiaa ahvagvfsle dactlvaara slmqqlprdg
7101 amvaleated evaplltdgv alaavngprs vvvagaedav ravadrlaad
7151 grrtrrltvs hafhsplmdp mltdfarvae gltyheprip lvstllgapa
7201 gaelrtpdyw vrhvretvrf adgvralhda gagtfveigp dgvltaltqq
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7301 gghrtdlpty afqrerywpe lgapvatapq dpaawryhet waplpapeaa
7351 apagralvlv pagnrdtawm tavadalgad tvtaepdala eqltaagdtp
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7501 pgteaeiavr atgvharrlv rtpaaadgat wlptgtvlvv ggtggtgtmg
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7701 avawgawadl vgpslaahlr mnglpvmdad taltalsrav adgsaaeava
7751 dvrwetfapl hhearrtalf dalpeargal aeaardradr ktaagdygrw
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7851 dlrnqltaet gltlpatlvf dhpnpaalaa hlraqllgea sdsaapvaap
7901 valgadddai vivgmacryp ggvtspedlw qlvgdevdav gdfptdrgwd
7951 laalagdgpg rsataqggfl ydatdfdpgl fgisprealv mdpqqrille
8001 tswealerag idpatlrgsg ttgvfvgggs gdyrppeeag qwqtaqsasl
8051 lsgrlaytfg iqgptvsvdt acssslvalh laaqalrage csialaggvt
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8201 idaveahgtg trlgdpieaq allatygqdr erpvllgslk snightqaas
8251 gvggvikmvl amqhgelprs lyaenpsshv dwtagrahll tartpwpdsg
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8501 rlieswgvrp dfvaghsvge laaahvagvl slddacrlva araalmqrlp
8551 aggamiavea tedevtpllt dgvslaavng ptavvlsgag davtalgqal
8601 aerghrttrl rvshafhshl mdpmladfrt vaegleyhpp ripvvsnltg
8651 dvadaadlcs adywvrhvrg tvrfadgvrt madrgvhlfl elgpdavlsa
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8801 alesvldves dalskvlpal mdwrsrqade sqlagwrhri vwkrltgaal
8851 ahrkalsgtw lavvpegfad dpwvtttldg lgthlvhlev aeadraalad
8901 aiaartadgt rfggvislla lreeltgavp egtaltttll qalgdagvda
8951 plwcvtrsav sagrtdrphr plqgavwglg rvaaleypqr wgglvdlpee
9001 pdersaagla avlagldged qvavrgtavl arrlvpapgr kpsrpwhpsg
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9101 gtdvtvaacd vadrdqltav ldalpadrpl tgvvhtagvl ddgvldrltp
9151 erfqevfrak vtsaslldel trdrelaafv lfssasaavg npgqanyaaa
9201 navldalaeq rrvlglpats vswgawgggg madadgadea arragvgamd
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9351 vaaersfrdl gvdslgavel rnqlsaatgl nlpatlvfdh ptplvlgehi
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SEQ ID NO. 38

NysJ

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251 efsrqgglar dgrckafada adgtgwsega gvlllerlsd aqrnghpvla
301 vvrgsavnqd gasngftapn gpsqqrvirq alanaglatg didaveahgt
351 gtplgdpiea qsilatygqd rahpvllgsi ksnmghtqaa sgvagvikmi
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551 ltawlahgta pdaheghaag rtrcaalfsg qgaqrlgmgr elharfpvfa
601 raldtavdll daelggtlre viwgtddapl netgftqpal favevalyrl
651 ieswgvapdf vaghsigeia aahvagvfsl edactlvaar aglmqalprg
701 gamvaveate devsplltdg vaiaaingpt slvvsgdeta tlavaarlae
751 qgrrttrlrv shafhsplmd pmlaefrava eglsygepqi pvvsnltgav
801 adgtllgtad ywvrhvreav rfadgiralt dagvgaflel gpdgtlaala

851 qqsapdavsv pvlrkdrdee paavaalarl htagvpvdwt afyagtgahr
901 tdlptyafqy erywpkatyr padatglglt aadhpllgaa msvagsdell
951 ltgtlslath pwladhvvgg mvffpgtgfl elavraadqv gcdrveelml
1001 aaplilpatg tvqmqiavga adddggrdlr fftrpgddpd aawaqhatgr
1051 itegervlal dtttwpprda epvdidglyd ryrangldyg pvfrglravw
1101 rrdteiyaev alpegtadad afglhpalfd avlhstlfas adgddrsllp
1151 fawngvslha agadalrvri tscgpdavei tavdpqgrpv vsvesltlra
1201 agpdagtadh radagslfrm dwtprtvhap atpatwavlg tdpiglteal
1251 taagpdtvtg lrdgvdalge ltagddrpvp dvvavplrga tdhgpagahd
1301 ltrtvlallq ewlaeerfar srlllvtrga vadgergpld laaapvwglv
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1451 vgiraaglnf rdvlnalgmy pgdaglfgse aagvvvevgp evtglapgdr
1501 vmgmlfggfg plgiadarll tpvpadwswe tgasvplvfl tayyalkelg
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1601 ddhiassrtl dfeaafaeva gdrgldvvln alsgefvdas mrllgdggrf
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1701 alpvrswdvr rageafrfms laqhigkivl tvpqpldpdg tvlltggtgg
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1901 hrhalglpat slawgaweqg agmtgaltdh dlrrvsdagg qplltaergl
1951 alydaataad eplivplglt ggalpagvgv pavlrglvrt agrraragta
2001 gvsraglaer laalpeeert pflvelvrte aatvlghgst dpvdarrefr
2051 qlgfdsltai elrnrlgkat gltlpatlif dyptpdrlav hlhdellgad
2101 apvtvtaaaq aadpehdpvv ivgmscrfpg gvsspeelwd lvasgtdait
2151 gfpadrawdr hpqlagapga rtgqggflrd iadfdaaffg isprealamd
2201 pqqrilleva weaaeragid pqtlrgsdtg vfmgvsgqdy aglvmrsrdd
2251 iaghattgla vsvvsgrlay alglegpals vdtacssslv slhlaaqalr
2301 agectmalag gvtvmttaan ftgfsrmggl aqdgrckafs dsadgtgwse
2351 gaavlvlerl sdarraghrv lavvrgsavn qdgasnglta pngpaqqrvi
2401 rqalanaglt pvdvdaveah gtgtplgdpi eaqaliaayg tdrdpehpll
2451 lgsvksnigh tqsaagaagl vkmvmamrhg ilpqtlhlte psshvdwsag
2501 tvrllterta wprtdrprra gvssfgisgt nahvileqpp aeptpaadpg
2551 rpaptvvawp vsaqtpaald aqldrlrtaa alapldtaht latgrslfeh
2601 ravllatvgd patgapdlpe vargaatphr taflfsgqga qrsgmgrelh
2651 aafpvfaaaf devvavldae lgsdadggvs lrevmwgggs elldrtrftq

2701 palfaveval frlvaswgvg pefvaghsvg eiaaahvagv fslvdacrlv
2751 varaslmdal pvggvmvave aaeaevvpll vdgvaiaavn gpvsvvvsgv
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2851 pripvvsnvt gevaaaeelc aadywvrhvr atvrfadgvr tlaergataf
2901 leigpdgvls alargvlpae alvtptlrkd rdeesallag larlhvagvt
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3101 aalaalltea addtaptavv sllaldetsg ddavpagtta taalvqalad
3151 tgapaplwal trgavaalpd eqptapaqaa vwglgriaal elprhwgglv
3201 dlpadldert arrlpaalad agdedqlalr atgaygrrit papapddapg
3251 tgwqptgtvl itggtgalgr htarwlaahg aehllllsrs gpdapgaael
3301 tteltalgar vtlvacdaad reqltrvlae vprdcpltgv vhtagvlddg
3351 vltgltpdrf atvfrakvas avlldeltrd tdlavfalfs svagavgnpg
3401 qagyaaanav ldalaarrra qglagtsiaw gawagdgmaa rhtrpgaepv
3451 glldpdlavp alaravtepq ptlvladlqq prllesllal rpspllsrlp
3501 aartaaravq eadrrragaa adlrdqlagt apadrhavll rlvrttaaav
3551 lghtgadair adkpfrdlgf dsltavelss alaaatglal ppslvfdhps
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3701 aafdpgffdi sprealamdp qqrllletaw eavertgtdp trlrgsrtgv
3751 fvgtngqdya glvlraqedv eghagtglaa svisgrlaya fgfegpavtv
3801 dtacssslva lhwavqalra gecslalagg vtvmttstsf agftrqggla
3851 pdghckafsd sadgtgwseg vgvlvverrs dalrngheil avvrgsavnq
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4051 ahvileqppa eptptapadr ptrtpavlpw vvsarsatal daqlarlraf
4101 aaerpdlppa dvahslvtsr atfehravll aapdgitaaa raearersta
4151 flfsgqgaqr sgmgrelhaa fpvfaaafde vvavldaela tgsgggvslr
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4301 gvaiaavngp vsvvvsgvea avgqvvdqlv ergrrvrrla vshafhsplm
4351 dpmldafrav aegleyhqpr ipvvsnvtge vaaaeelcaa dywvrhvrat
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4551 eadgrtvlpa avlaelavra gdqadcptva eltvaaplvl tgaaaqrlqv
4601 rvaapddtgr ralsvharpd dspdspwtlh atavlthdtp qppapdtgwp
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4701 lldtavragg lldgdatlda lgwrglalha asatalrvrl tpdgtdtwal
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4851 apvlgvptge gdlpaavrgt ttavlellqr wtadartads hlvivtrgav
4901 aagaedvhdl aaapvwglvr saqsehpgsf llldldpadp agasraaapa
4951 tlaalldage tqaavradtl tvarltraad gpeataghpv rdwdrdgtvl
5001 itggtgglgg llarhlvtgh gikhlllagr rgpdapgara lrdelaalga
5051 evtvaacdva draaldrlla qlppehplta vvhtagvldd atvgtltper
5101 ldtvlrakad aawhlhdatr drdlagfvly ssvagvtggp gqgnyaagnt
5151 fldalaahra aqglpglsla wgpwgqdagm tgtlgaadla rlersgmppl
5201 tpeqglalfd aagargdgfa vavrlargaa apgadevpav lralvrgrrr
5251 taaaaghagv larrlaalda eqrhqalldl vrtetaavlg hsgadavpae
5301 rdfnrlgfds lmavelrtrl atatgarlpa tlvfdhptpd avarhlastl
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SEQ ID NO. 39

NysK

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101 afdpgffdis prealamdpq qrllletawe aversgidpa glrgsrtgvf
151 vgtngqdyah lvlaaqddmg gyagnglaas vlsgrlafal glegpavtld
201 tacssslvtl hlaaqavrag ecglalaggv tvmttsssfa gfslqgglap
251 dgrckafaea adgtgwsegi glllverlsd aqrnghpvla vlrgsavnqd
301 gasnglsapn gpsqqrvirq alagaglvpg dvdaveahgt gtrlgdpiea
351 gallatygqd rpadrplwlg svksnlghtq aaagvagvik mvlalrhgvl
401 pqtlhvdaps shvdwesgav rlltapvaws egddrvrrag vssfgisgtn
451 ahvileqapd qpeptaeeta aaapggtaee raaapvapra vpwpvaarta
501 galdaqlvrv ralttapgrt aadvghalat artpfehral lvheggavte
551 vargavptgd rgglavlfsg qgsqrpgmgr elharypvfa aafdetvall
601 darlgtslrd ivwdqdrtrl ddtrhtqpal favevalyrl laswgirpdh
651 vtghsigeit aahvagvltl adactlvaar atamselppg gamvaleate

701 devrplltdd laiaavnapr svvvagaeda alavrrhfdd lgrrttrlpv
751 shafhsplmd pmldafrtal apltfaepei pvvsnltglp ataeelatph
801 ywvchvrqav rfgdgvrala drgvrtflel gpdgvlsalv renlpepglv
851 avpvlrkerp eettvlaalg tlwahgadvd wdavfagtrt pqadpvelpt
901 yafqrarywp tlgarhgdpa dlgqtaaahp llgaavtlad adetvltgrl
951 alpshpwlgd hrsdgritvp gvafaelavr agdlsgtphl arldlpaplt
1001 lgdgdtvtlq vrvgapdpag hrpltvharl aatedapwtt catgllapda
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1101 rrdgevfaev alptataadr afgihpalla talrataald ddhtaghtpe
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1301 ralgllqewl neprlagarl vfvtrgavav pgetvtdpag aavwgllrsa
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1701 vgytagllgh pdptavdper gflelgfdsl vsvglrnqla eilglrlpss
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1851 fvsapgatgg vhqyariaah frgsrhvsal plmgfapgel lpatseaaar
1901 ivaesvlmas egepfvmvgh stggslayla agvledtwdv rpeavvlldt
1951 asirynpgeg ndldrttrfy ladidspsvt lnsarmsama hwfmamtdiq
2001 apaptaptll vraaraldgf rldtssvpad evrdidadhl slakehsalt
2051 aqaiegwlae lpdpaa

SEQ ID NO. 40

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101 slftpqfsar rvmdltprvc alaegvlahf vaqgppadlh ndfslpfsls
151 vlcaligvpa eeqgkliaal tklgelddpa rvqegqdelf gllsglarrk

201 ritpeddvis rlclkvpsde rigpiasgll fagldsvash idlgtvlfiq
251 hpdqlaaala deklmrgave eilrsakagg svlpryatad vpigdvtira
301 gdlvlldftl vnfdrtvfde pelfdirrap nphltfghgm whcigaplar
351 vnlrtaytll ftrlpglrlv rpveelrvls gqlsagltel pvtw

SEQ ID NO. 41

NysM

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51 aalcpsgais vaad

SEQ ID NO. 42

NysN

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201 rylgrliqik qrrpgddlis rliaagtlsr qelsgvamll liaghettan
251 niglgvvqll tnprwigddr iveellryys vadlvafrva vedveiggql
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351 lvreemdiay rtlfaripsl tlavpveelp lkydgvlfgl helpvtwk

SEQ ID No. 43:

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SEQ ID NO. 44:

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SEQ ID NO. 46:
CTC AGC ATG CCG AAA GGA TGG CGG

SEQ ID NO. 47:
AGG CAA GCT TCG GCG ACA CGG GCG T

SEQ ID NO. 48:
CTC AGC ATG CGT ACG ACC GGC GGG

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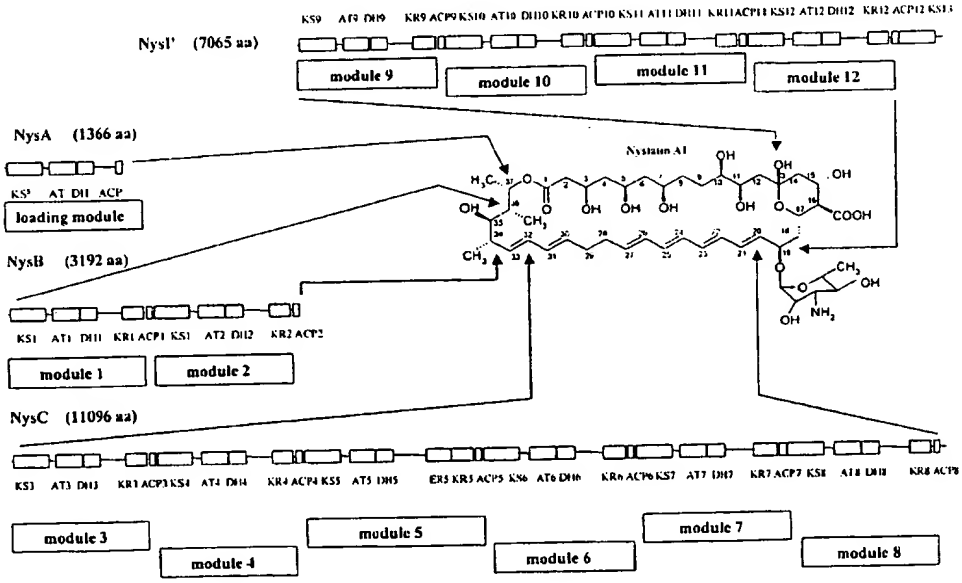
[Continued on next page]

(54) Title: GENE CLUSTER ENCODING A NYSTATIN POLYKETIDE SYNTHASE AND ITS MANIPULATION AND UTILITY



(57) Abstract: The invention provides a nucleic acid molecule comprising: a nucleotide sequence as shown in SEQ ID No. 35; wherein said sequence preferably encodes or is complementary to a sequence encoding a nystatin PKS enzyme or a part thereof. Also provided are part of such molecules and polypeptides (and parts thereof) encoded by such a nucleic acid molecule, and the use of such molecules and polypeptides in facilitating nystatin biosynthesis and in the synthesis of nystatin derivatives and novel polyketide as macrolide structures.

WO 01/59126 A3

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INTERNATIONAL SEARCH REPORT

Ir ational Application No
PCT/GB 01/00509

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/52 C12P17/18 C12P19/62 C07H17/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C12P C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBL, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EM_PRO 'Online! EMBL; ID SNA132222, AC AJ132222, 20 April 1999 (1999-04-20) APARICIO J F: "Streptomyces natalensis pimS1 gene" XP002174375 Note: 60.5%, 60.4% and 60.5% nt seq identity with SEQ ID NO:35, 1 and 2 in 6853, 5454 and 6853 nt overlap (5017-11675:6892-13554, 5974-11277:29502-34804, and 5017-11675:6892-13554), respectively page 4-5	1-7,9, 14,17, 19-24, 27,30-36
X	-& APARICIO J F ET AL.: "The biosynthetic gene cluster for the 26-membered ring polyene macrolide pimaricin: A new polyketide synthase organization encoded by two subclusters separated by -/--	1-7,9, 14,17, 19-24, 27,30-36

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
8 August 2001	22/08/2001

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	functionalization genes." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 274, no. 15, 9 April 1999 (1999-04-09), pages 10133-10139, XP002174372 abstract page 10139, left-hand column, line 12-14 ---	
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X	DATABASE SWALL 'Online! SWISSPROT; ID Q9X9X5, AC Q9X9X5, 1 November 1999 (1999-11-01) SEEGER K ET AL.: "PUTATIVE TRANSCRIPTIONAL REGULATOR" XP002174377 Note: 65.6% aa seq identity with SEQ ID NO:13 in 250 aa overlap (9-258:4-253) the whole document ---	1-6,14, 15
X	SHENIN Y D ET AL.: "Nystatin: Methods for preparation, search for derivatives, and prospects for application in medicine (review)." KHIMIKO-FARMATSEVTICHESKII ZHURNAL, vol. 27, no. 2, 1993, pages 14-21, XP000984316 ISSN: 0023-1134 the whole document figure on page 17 ---	35,36
X	US 5 981 721 A (MOHAN ARTHUR G) 9 November 1999 (1999-11-09) the whole document example 12 --- -/--	35,36

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	KHOSLA C ET AL: "Generation of polyketide libraries via combinatorial biosynthesis" TRENDS IN BIOTECHNOLOGY, vol. 14, no. 9, 1 September 1996 (1996-09-01), pages 335-341, XP004035738 ISSN: 0167-7799 the whole document ---	23-28, 30-36
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/00509

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SEKUROVA O ET AL: "Molecular cloning and analysis of a pleiotropic regulatory gene locus from the nystatin producer Streptomyces noursei ATCC11455." FEMS MICROBIOLOGY LETTERS, vol. 177, no. 2, 15 August 1999 (1999-08-15), pages 297-304, XP001015583 ISSN: 0378-1097 cited in the application abstract	
A	VANDEN BOSSCHE H ET AL: "Anti-Candida drugs - the biochemical basis for their activity" CRITICAL REVIEWS IN MICROBIOLOGY, vol. 15, no. 1, 1987, pages 57-72, XP001015427 ISSN: 0045-6454 paragraphs I and II	
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T	ZOTCHEV S ET AL.: "Identification of a gene cluster for antibacterial polyketide-derived antibiotic biosynthesis in the nystatin producer Streptomyces noursei ATCC 11455." MICROBIOLOGY, vol. 146, no. 3, March 2000 (2000-03), pages 611-619, XP001012427 ISSN: 1350-0872 the whole document	

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Ir ational Application No
PCT/GB 01/00509

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